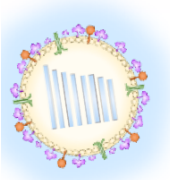




Host regulators of the influenza virus replication machinery



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Department of

MEDICAL MICROBIOLOGY & IMMUNOLOGY

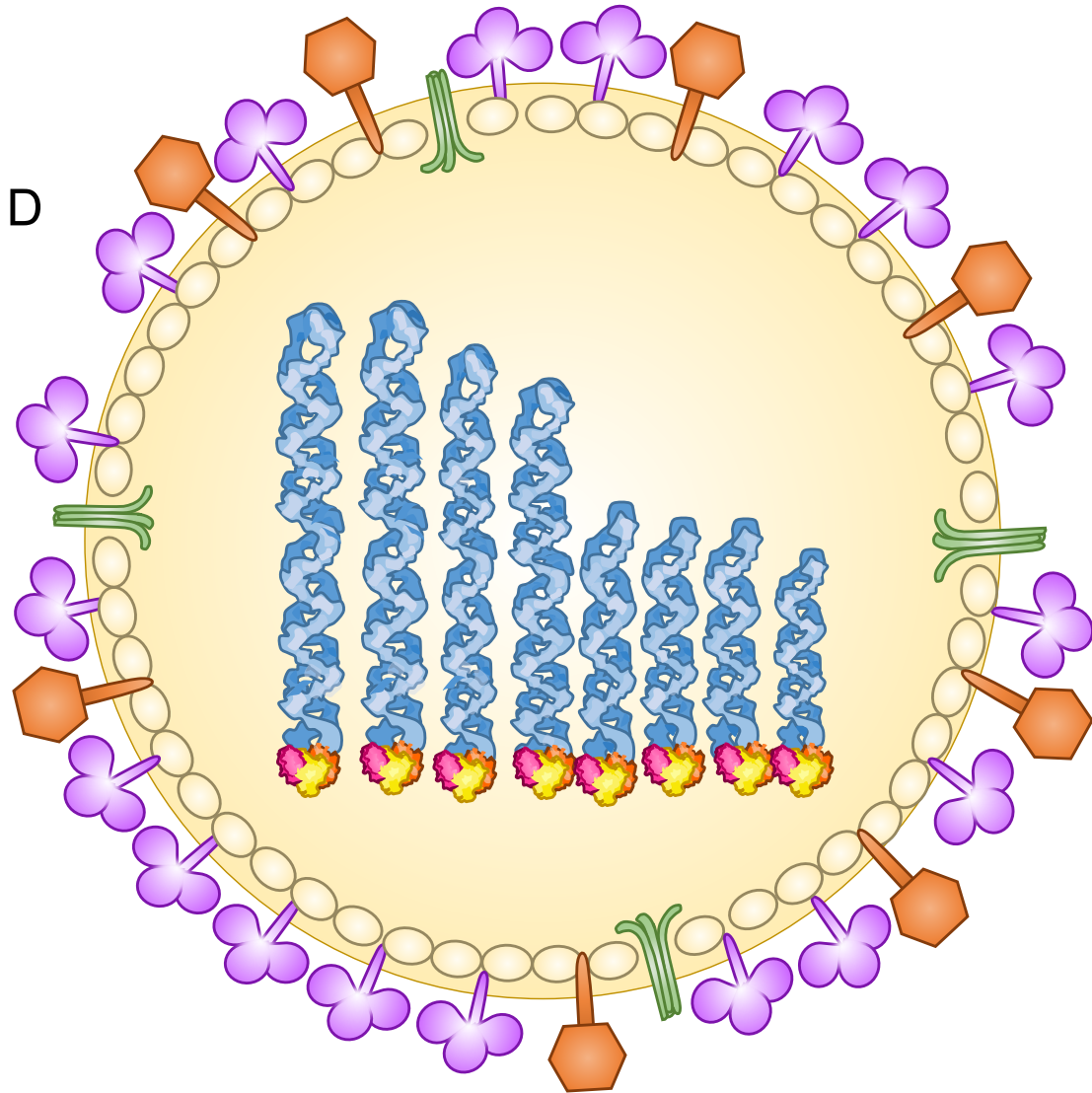
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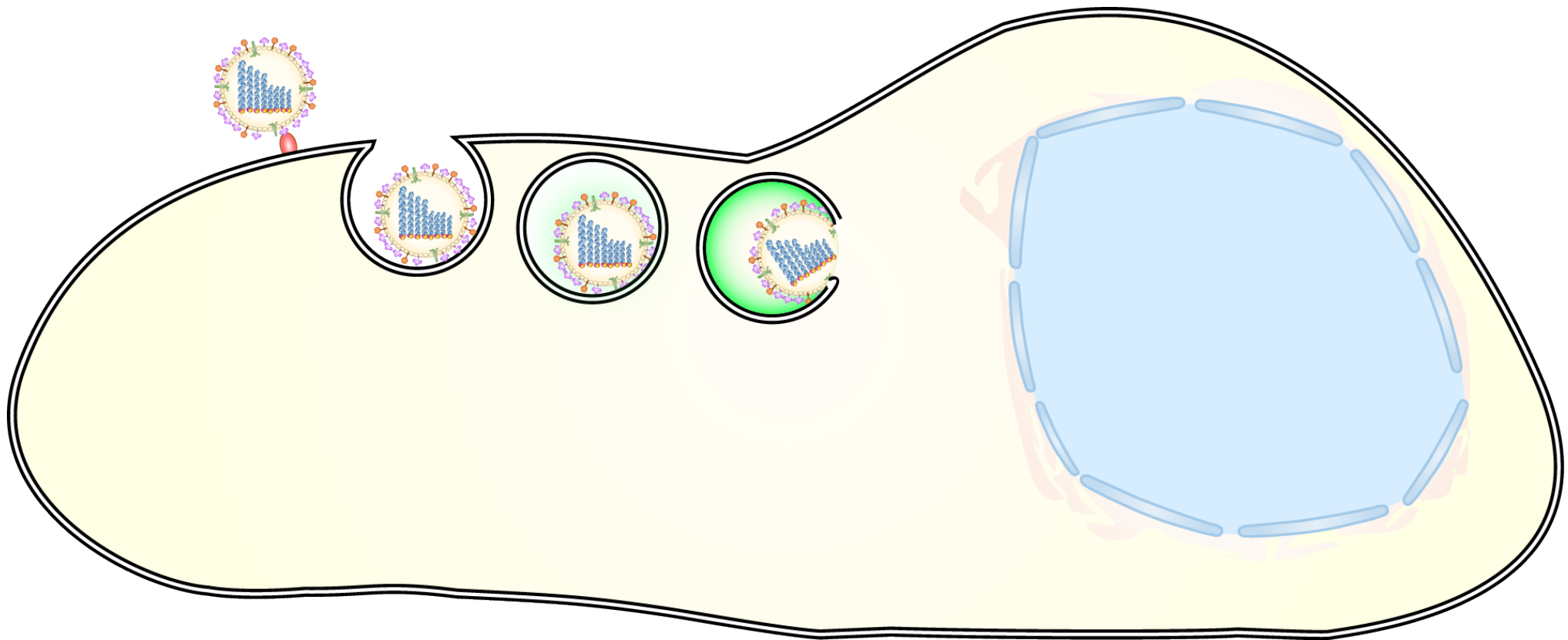


Influenza viruses

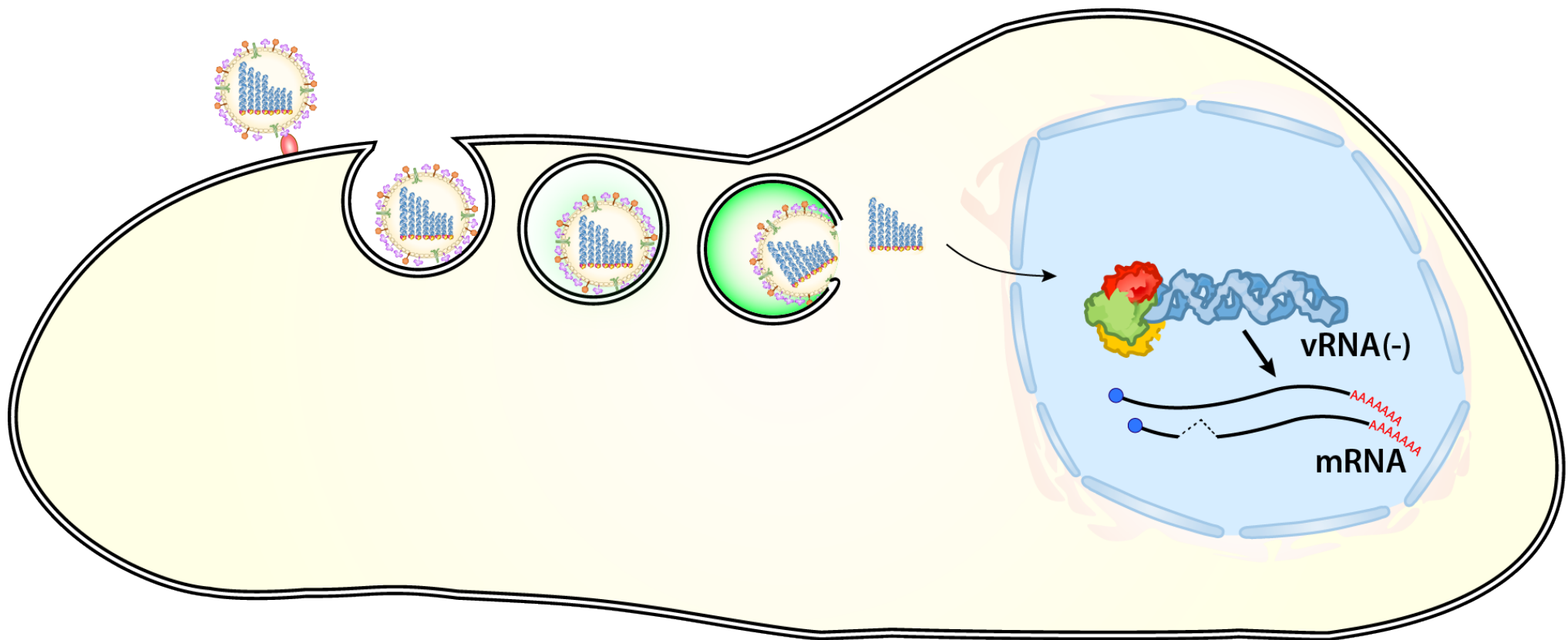
- *Orthomyxoviridae*: Influenzas A, B, C, D
- Surface HA and NA define influenza subtypes (18 HA, 11 NA)
- Negative-sense ssRNA genome
 - 8 segments, ≥ 14 proteins
 - Packaged into ribonucleoprotein complexes (RNPs)



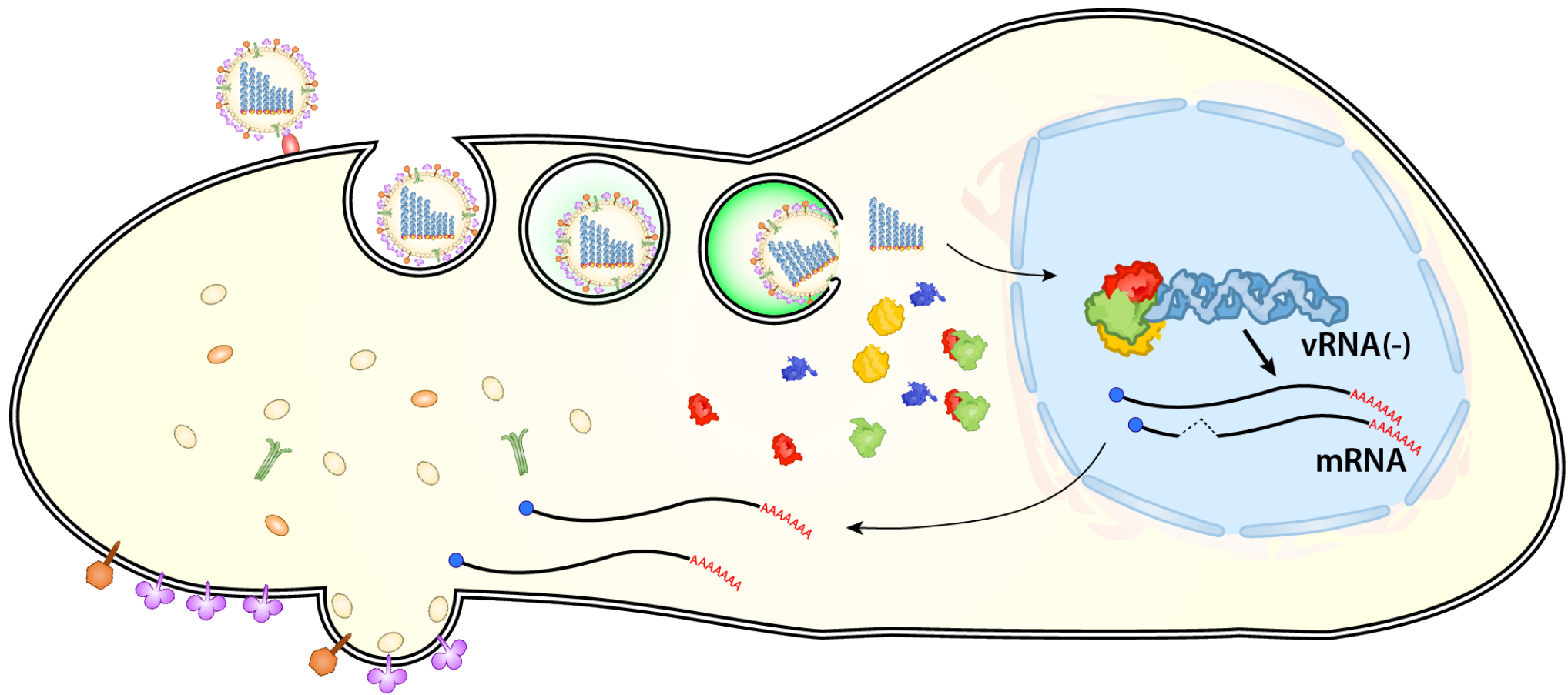
The influenza virus replication cycle



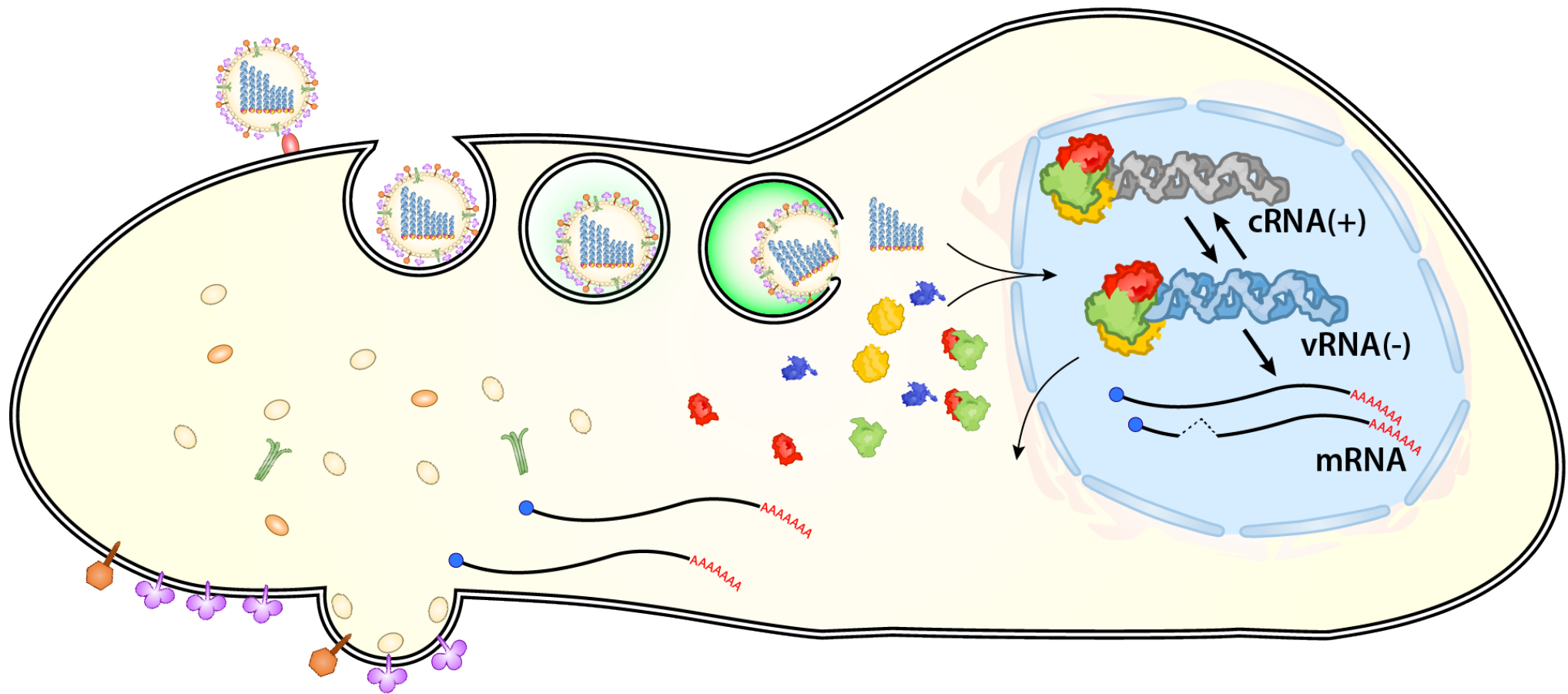
The influenza virus replication cycle



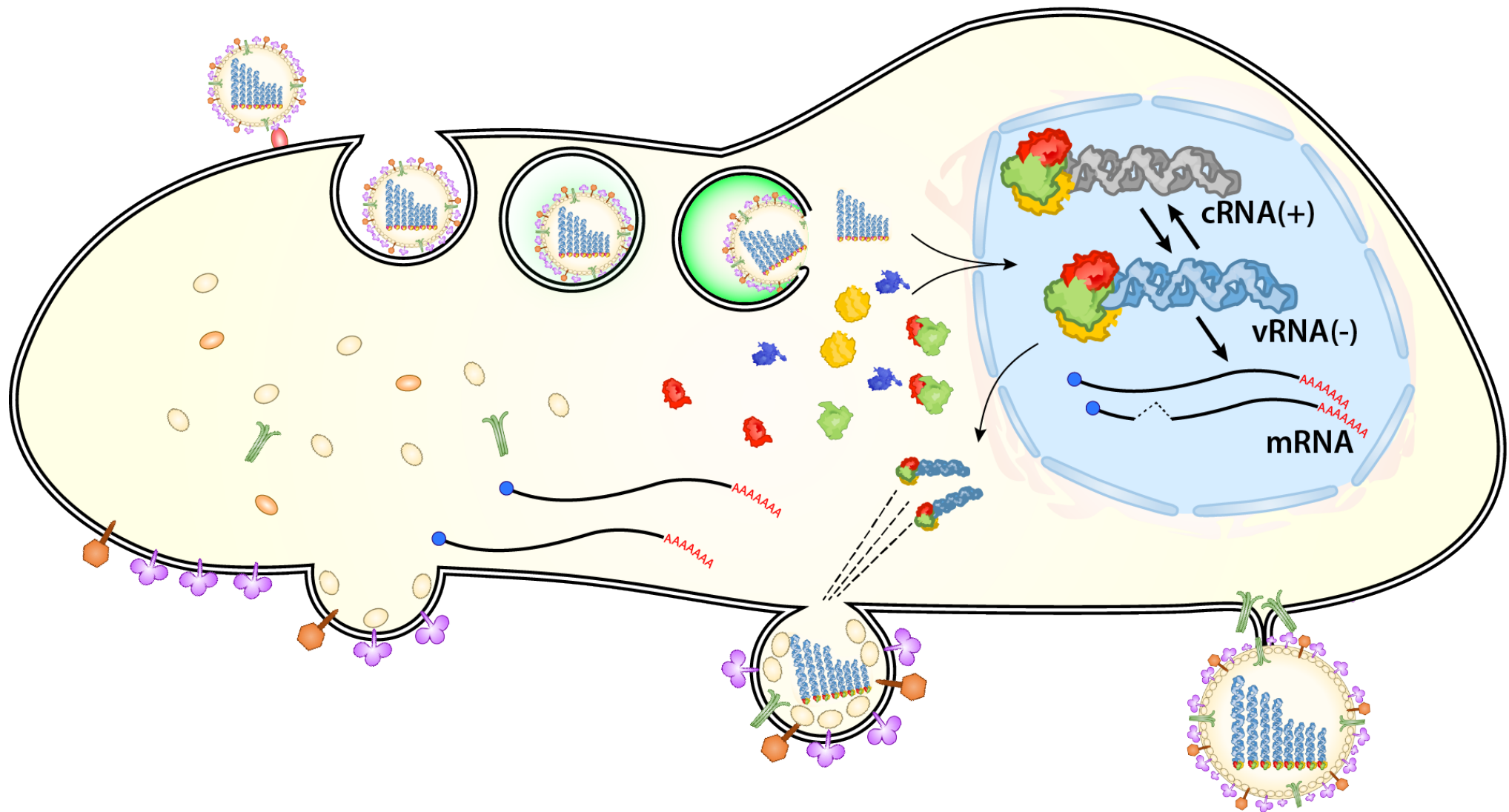
The influenza virus replication cycle



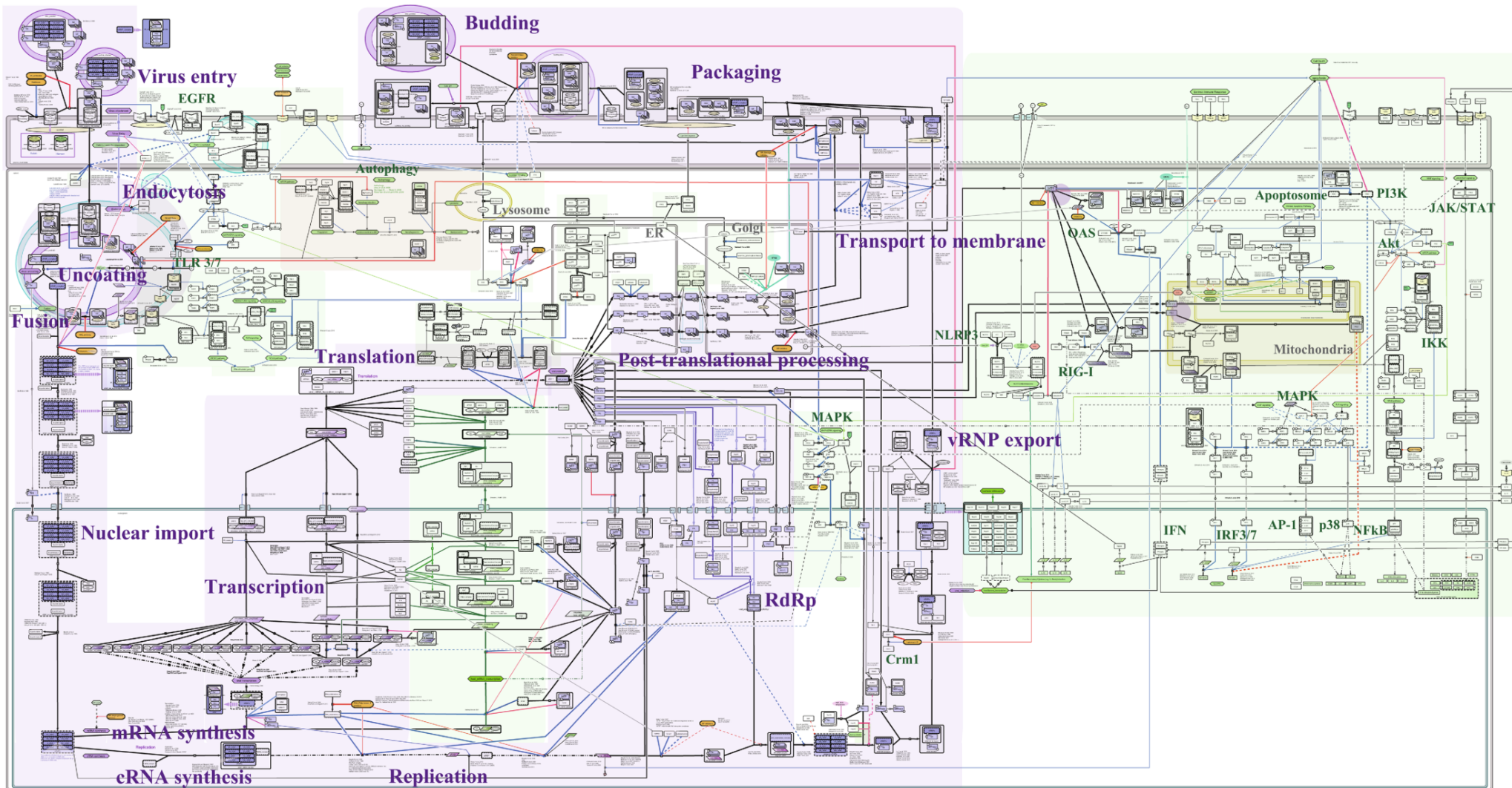
The influenza virus replication cycle



The influenza virus replication cycle



The influenza virus replication cycle



Virus-host interactions determine replication efficiency, transmission, disease

Genome-wide screens to identify host factors

Functional Genomics

RNAi

Hao (2008)
Brass (2009)
Karlas (2010)
König (2010)
Ward (2012)
Tran AT (2013)
Su (2013)

Haploid Selection

Carette (2009)

Random Homozygous Gene Perturbation

Sui (2009)

Meta-Omics

Tripathi (2015)
Tisoncik-Go (2016)



~20,000 human genes

Proteomics

Y2H

Shapira (2009)
Tafforeau (2011)
Fournier (2014)

IP/Pulldown + MS

Mayer (2007)
Jorba (2008)
Shaw (2008)
Bradel-Tretheway (2011)
Kawaguchi (2012)
York (2014)
Watanabe (2014)
Heaton (2016)

Protein Complementation

Munier (2013)

Others...

RNAi:AATK, ABCB10, ABCC10, ABCC6, ABCD1, ACACA, ACE2, ACOX1, ACP2, ACR, ACSL1, ACSL4, ACTC1, ACTL6B, ACTN2, ACVR1C, ACVR2A, ADAM8, ADAMTS1, ADAMTS2, ADAMTSL4, ADAT1, ADCY7, ADRA18, ADRB2, ADRBK2, AFF2, AGTRAP, AHCY, AHCYL1, AHNAK2, AHR, AIG1, AKAP11, AKAP13, AKT1, AKT3, ALA51, ALG10, ALG6, ALPK2, AMHR2, AMMECR1, AMN, AMOTL1, AMOTL2, ANAPC2, ANGPTL3, ANKK1, ANKMY2, ANKRD2, ANKSE, ANPEP, AP2B1, AP2M1, APB3A, APBB1A, APC, APC2, APOA1, APOA5, APOBEC3G, APOLE, AP, APPBP1, APO4, AQR, ARAF, ARCN1, ARD1, ARLA4, ARMC6S, ARNT, ARNT, ASAH1, ASPL, ASCA, ATFB, ATF2, ATFA, ATG16L1, ATP13A1, ATP1A2, ATP1A3, ATP2C1, ATP5B, ATP5C1, ATP5F1, ATP5L, ATP6A1, ATP6A2, ATP6VB, ATP6VC, ATP6VD01, ATP6VOE2, ATP6V1A, ATP6V1B, ATP6V12, ATP6V14, ATP8, AXIN1, X2N, B3GALT2, BACE1, BACH2, BAIDP, BAIDP1, BAIR, BARN, BARKHL2, BCAS2, BCL10, BCL1, BCL2, BCL6, BID, BIRC1, BIRC8, BLNK, BMPR1A, BMPR1B, BMPR2, BRPF1, BRWD3, BST2, BTG1, BUB1B, BUB3, BZRAP1, C10orf57, C11orf60, C11orf82, C12orf47, C12orf5, C14orf109, C14orf166, C14orf169, C14orf172, C14orf28, C14orf94, C16orf72, C19orf20, C19orf29, C1GALT1, C1orf159, C1orf222, C1orf55, C1orf94, C15, C20orf111, C20orf54, C21orf121, C21orf33, C21orf72, C21orf82, C21orf91, C22orf15, C2orf32, C2orf42, C2orf69, C3orf38, C5orf6, C6orf33, C6orf62, CA13, CACB1, CABIN1, CACNA1A, CACNA1C, CACNB1, CACNB3, CACNB4, CACNG1, CACNG4, CACNG7, CAD, CADM1, CADM2, CALCOCCI, CALCOCC2, CALM2, CALML3, CAMK2B, CAMK2G, CANT1, CAPN6, CARD10, CARD16, C2ASBP3, CASP9, CBL1, CBX2, CDCD12, CDCF24A, CDCF47B, CDCD78, CCL13, CCL2, CCL26, CCL3, CCL3B, CCLN1, CCRK, CCRNL4, CD3EAP, CD47, CD48, CD58, CD81, CD83, CD82, CDC42BP4, CDC42BPB, CDH11, CDK10, CDK4, CDK5RAP2, CDKL5, CDKN1B, CDKN2A, CDKN2C, CEACAM7, CEBPA, CEBPD, CEL, CENTA1, CENB2, CFLAR, CH25H, CHAC1, CHAF1A, CHMP2B, CHMP6, CHRM1, CHST5, CHUK, CIRBP, CISH, CT, CKS1B, CLCF1, CLEC2B, CLN, CLK1, CLK3, CLK4, CLN5, CLOC, CLSTN3, CLU, CLUAP1, CNGB1, CNMN1, CNOT10, CNOT3, CNP, CNTNS, COL1A1, COL2A1, COPA, COPB, COPB1, CPB2, COPE, COPE, COP56, COP21, COP26, COX6A1, CPLX1, CPN2, CPS4, CRADD, CRAMP1L, CREB1, CREBB, CREBL2, CRHR1, CRKRS, CRKL1, CRSP2, Cry2, CRYDAS, CE1L, CSEN, CSF2, CSMD3, CSNK1A1, CSNK1A1E, CSNK1A2, CSNK2A2, CTBP1, CTDSPL, CTGFP, CTN1, CTN, CTNNB1, CTNNB1L, CTNNB1L1, CTSG, CTSW, CUL1, CUTC, CWC22, CXCL31, CXCL1, CXCL10, CXCL9, CXCR6, CxorF21, CxorF40A, CxorF59, CYBSR4, CYCS, CYLD, CYP71A1, CYP2J2, CYP2U1, DAAM1, DAAM2, DAP, DAP3, DAPK2, DAPK3, DAXB, DAXT, DEAFM12, DCLK1, DCLK2, DCLRE1A, DCLRE1B, DCLRE1C, DCP2, DDAH1, DXD48, DERL3, DFFB, DGKD, DGKG, DHC2A, DHC2R, DHRS2, DHX2, DIO1, DKK1, DLG2, DLG5, DLX2, DMAP1, DM2, DMLX2, DNAJB9, DPF2, D5C3, D5D, DTX2, DTX3, DUPD1, DUSP1, DUSP2, DUSP5, DUSP6, DVL3, DYNCH11, DYRK1B, EZF1, EZF2, EAF2, EAF2A, EIF2A2, EIF2AK3, EIF2AK4, EIF25A, EIF252, EIF35S2, EIF35S3, EIF35F, EIF357, EIF4A2, EIF5, ELK1, ENG, ENSG00000174121, ENTDPD, EP300, EPHA4, EPHA7, EPHB2, EPXB, EPHB6, EPRS, EPS81R, ERC1, ERCC4, ERLIN2, ERN2, ESAM, ETHE1, ETS1, EVCC, EXT1, F13A1, F2R, FADS2, FADN1048, 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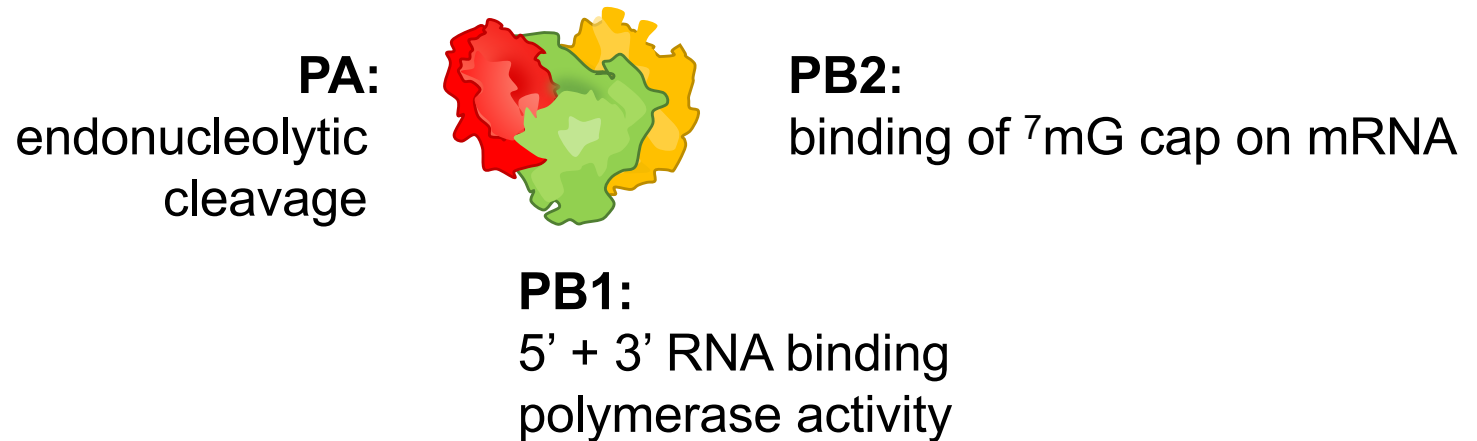
Overview of host regulators of the influenza virus replication machinery

ADRD7, TEAD3, TRAP2A	TFAP2C, TFD1, TFD2, TFE3, TGFBR1, TGFBR2, TGS1, TGM, TGM4, TIMM44, TIRAP, TK2, TKL1, TLR10, TLR2, TMEM110, TMEM111, TMEM167B, TMEM186, TMEM187, TMEM8, TMEM82, TMFN1, TNC, TNFAIP8, TNFRSF100, TNFRSF18, TNFRSF19, TNFRSF6, TNFSF11, TNIP3, TNK2, TNPO3,
TOBE2, TOP1M, TOP2A	OPORS, TP53, TPFR1, TPSAB1, TPST1, TPST1, TPST1, TRAF6, TRAM1, TRAP1, TRDMT1, TREM2, TREM7, TRIB1, TRIB2, TRIB3, TRIM12, TRIM21, TRIM25, TRIM26, TRIM27, TRIM28, TRIM60, TRIM62, TRPV2, TRRAP, TSC22D3, TSTA3, TTC12, TUBB, TUBB3, TUFT1, TULP4, TWIST1, TWIST, TXK, TXNDC1, TXNKLX4A, TYK2,
UBC, UBE2A, UBE2E1, U	BL5, UBPI1, UBLQLN4, UBR4, UBXD3, UBXN10, ULBP1, ULBP3, UMP5, UNCX, UQCRC2, UROS, URP2, USE1, USF2, USHBP1, USMG5, USP42, USP46, USP6, VAV2, VCP, VDR, VEGFB, VISA, VLDLR, VNN2, VPS16, VPS54, WAC, WASF1, WASF3, WDFY3, WDR18, WDR33, WDR34, WDR37, WEE1,
WNT9A, WNT9B, WTP4	KAB2, XAF1, XBP1, XBP, XPNPPE1, XPO1, XPO5, XR_019565.1, YTHDC1, XZ, ZBTB2, ZBTN3, ZCCHC8, ZFYVE26, ZIC1, ZKSCAN1, ZMAT3, ZMAT4, ZMI21, ZNF132, ZNF154, ZNF160, ZNF169, ZNF217, ZNF224, ZNF350, ZNF378, ZNF414, ZNF432, ZNF436, ZNF473, ZNF492, ZNF512, ZNF513, ZNF522, ZNF552, ZNF512B, ZNF513B, ZNF552, ZNF552,
ZNF567, ZNF653, ZNF8	AP-MS: AATF, ABCB1, ABCC1, ABCC2, ABCC3, ABCC4, ABCF2, ABCF3, ABHD12, ACACA, ACAC8, ACAD9, ACAT1, ACIN1, ACYL, ACOT9, ACSL3, ACSL4, ACSL6, ACTG1, ACTN1, ACTN2, ACTR1A, ACTR1B, ACTR2, ADAR, ADCK4, ADSL, AFG3L4, AGK, AGO2, AGPAT5, AGPAT9, AGPS, AHYCL1, AHYCL2, AHNAK,
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ATP5L, ATP5O, ATP6V2	AP2M1, APMAP, APOL2, ARCNI, ARF1, ARF3, ARF4, ARF5, ARFGAP1, ARGFEF1, ARGFEF2, ARGHEF10L, ARGHEF2, ARGHEF28, ARL1, ARLB8, ARMC6, ARSE, ASPI, ATAD3A, ATG6A, ATL2, ATL3, ATP1A1, ATP1A2, ATP2B1, ATP2B4, ATP4A, ATP5C1, ATP5F1, ATP5L, ATP5P1, ATP5P2,
C9ORF167, CA12, CAD	ATP5L, ATRN, ATXN10, ATXN17L3B, AUP1, B4GALT1, B4GALT4, BAG3, BAG3, BAG4, BAG5, BASP1, BUB1, BIRC6, BOP1, BRAT1, BRD8, BRSKI1, BTAFL1, BUB3, BYSL, BZW1, C14orf158, C14orf166, C16orf80, C17orf85, C18orf34, C19orf43, C19orf52, C2orf14, C6orf211, C7orf27, C
CDR6B167, CA12, CAD	CALR, CALI, CAND1, CANX, CAPN1, CAPN51, CAPRIN1, CAPRIN2, CAPZB1, CAPZB2, CAPZB, CASC3, CBAR2, CDC43, CDC42, CDC43, CDC44, CDC45, CDC58, CDC688C, CHCHD24, CCT1, CCT2, CCT3, CCT4, CCT5, CCE1A, CCT7, CCT8, CD59, CD97, CD123, CD2, CD23, CD24, CD24C2, CD24E1, CD28, CDK1, CD52, CD59, CD61, CD62, CD63, CD64, CD65, CD66, CD67, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CD75, CD76, CD77, CD78, CD79, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD87, CD88, CD89, CD90, CD91, CD92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107, CD108, CD109, CD110, CD111, CD112, CD113, CD114, CD115, CD116, CD117, CD118, CD119, CD120, CD121, CD122, CD123, CD124, CD125, CD126, CD127, CD128, CD129, CD130, CD131, CD132, CD133, CD134, CD135, CD136, CD137, CD138, CD139, CD140, CD141, CD142, CD143, CD144, CD145, CD146, CD147, CD148, CD149, CD150, CD151, CD152, CD153, CD154, CD155, CD156, CD157, CD158, CD159, CD160, CD161, CD162, CD163, CD164, CD165, CD166, CD167, CD168, CD169, CD170, CD171, CD172, CD173, CD174, CD175, CD176, CD177, CD178, CD179, CD180, CD181, CD182, CD183, CD184, CD185, CD186, CD187, CD188, CD189, CD190, CD191, CD192, CD193, CD194, CD195, CD196, CD197, CD198, CD199, CD200, CD201, CD202, CD203, CD204, CD205, CD206, CD207, CD208, CD209, CD210, CD211, CD212, CD213, CD214, CD215, CD216, CD217, CD218, CD219, CD220, CD221, CD222, CD223, CD224, CD225, CD226, CD227, CD228, CD229, CD230, CD231, CD232, CD233, CD234, CD235, CD236, CD237, CD238, CD239, CD240, CD241, CD242, CD243, CD244, CD245, CD246, CD247, CD248, CD249, CD250, CD251, CD252, CD253, CD254, CD255, CD256, CD257, CD258, CD259, CD260, CD261, CD262, CD263, CD264, CD265, CD266, CD267, CD268, CD269, CD270, CD271, CD272, CD273, CD274, CD275, CD276, CD277, CD278, CD279, CD280, CD281, CD282, CD283, CD284, CD285, CD286, CD287, CD288, CD289, CD290, CD291, CD292, CD293, CD294, CD295, CD296, CD297, CD298, CD299, CD300, CD301, CD302, CD303, CD304, CD305, CD306, CD307, CD308, CD309, CD310, CD311, CD312, CD313, CD314, CD315, CD316, CD317, CD318, CD319, CD320, CD321, CD322, CD323, CD324, CD325, CD326, CD327, CD328, CD329, CD330, CD331, CD332, CD333, CD334, CD335, CD336, CD337, CD338, CD339, CD340, CD341, CD342, CD343, CD344, CD345, CD346, CD347, CD348, CD349, CD350, CD351, CD352, CD353, CD354, CD355, CD356, CD357, CD358, CD359, CD360, CD361, CD362, CD363, CD364, CD365, CD366, CD367, CD368, CD369, CD370, CD371, CD372, CD373, CD374, CD375, CD376, CD377, CD378, CD379, CD380, CD381, CD382, CD383, CD384, CD385, CD386, CD387, CD388, CD389, CD390, CD391, CD392, CD393, CD394, CD395, CD396, CD397, CD398, CD399, CD400, CD401, CD402, CD403, CD404, CD405, CD406, CD407, CD408, CD409, CD410, CD411, CD412, CD413, CD414, CD415, CD416, CD417, CD418, CD419, CD420, CD421, CD422, CD423, CD424, CD425, CD426, CD427, CD428, CD429, CD430, CD431, CD432, CD433, CD434, CD435, CD436, CD437, CD438, CD439, CD440, CD441, CD442, CD443, CD444, CD445, CD446, CD447, CD448, CD449, CD450, CD451, CD452, CD453, CD454, CD455, CD456, CD457, CD458, CD459, CD460, CD461, CD462, CD463, CD464, CD465, CD466, CD467, CD468, CD469, CD470, CD471, CD472, CD473, CD474, CD475, CD476, CD477, CD478, CD479, CD480, CD481, CD482, CD483, CD484, CD485, CD486, CD487, CD488, CD489, CD490, CD491, CD492, CD493, CD494, CD495, CD496, CD497, CD498, CD499, CD500, CD501, CD502, CD503, CD504, CD505, CD506, CD507, CD508, CD509, CD510, CD511, CD512, CD513, CD514, CD515, CD516, CD517, CD518, CD519, CD520, CD521, CD522, CD523, CD524, CD525, CD526, CD527, CD528, CD529, CD530, CD531, CD532, CD533, CD534,

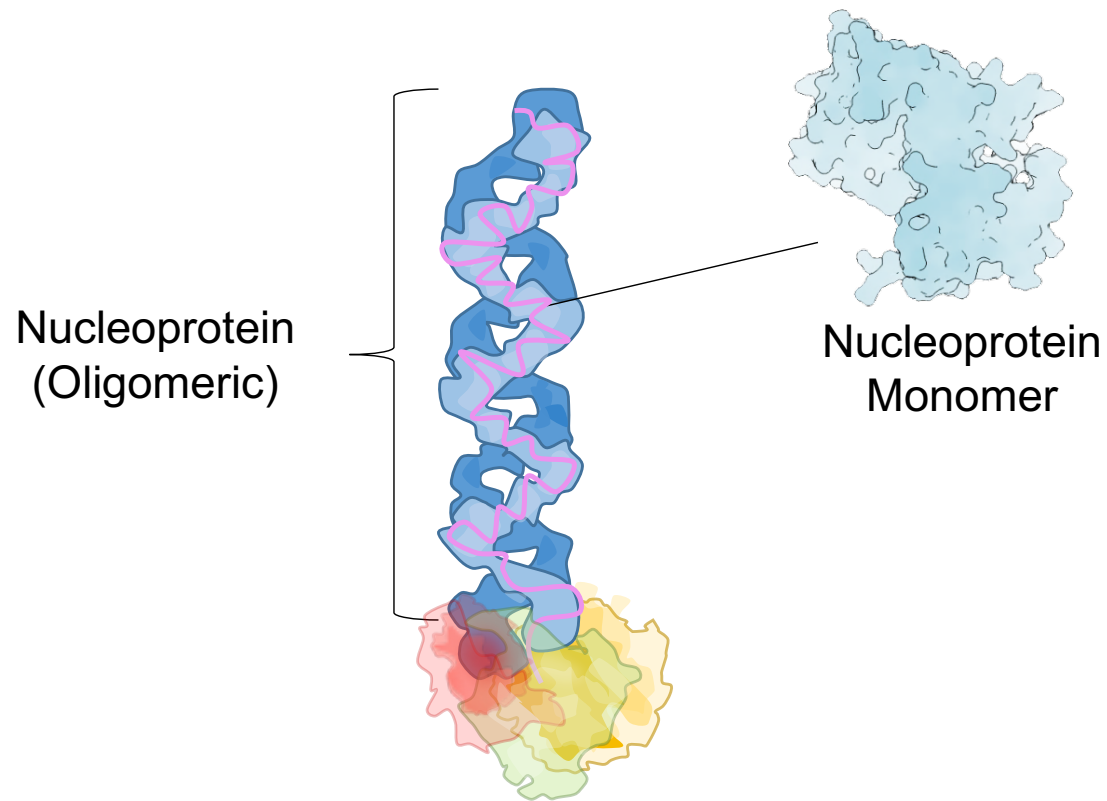
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[illegible]

The influenza polymerase

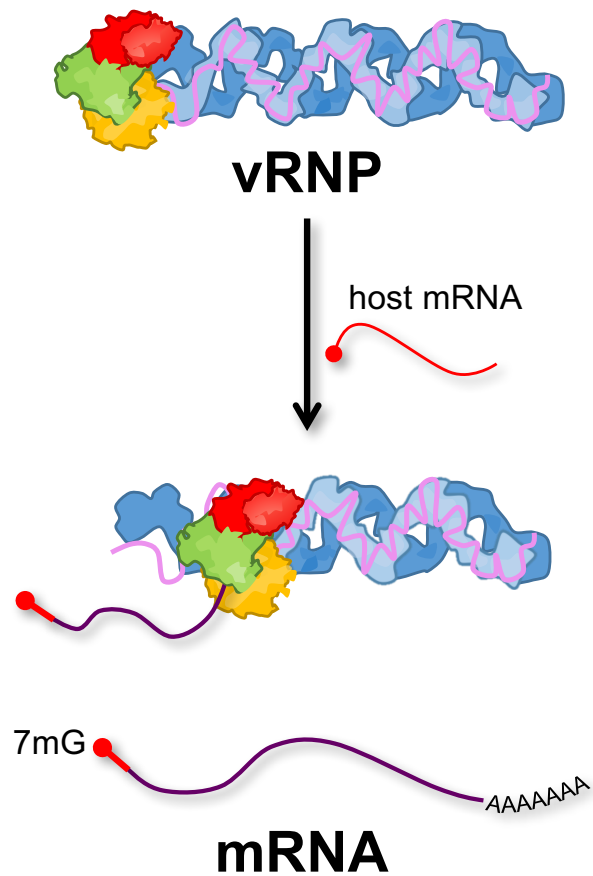


The influenza RNP

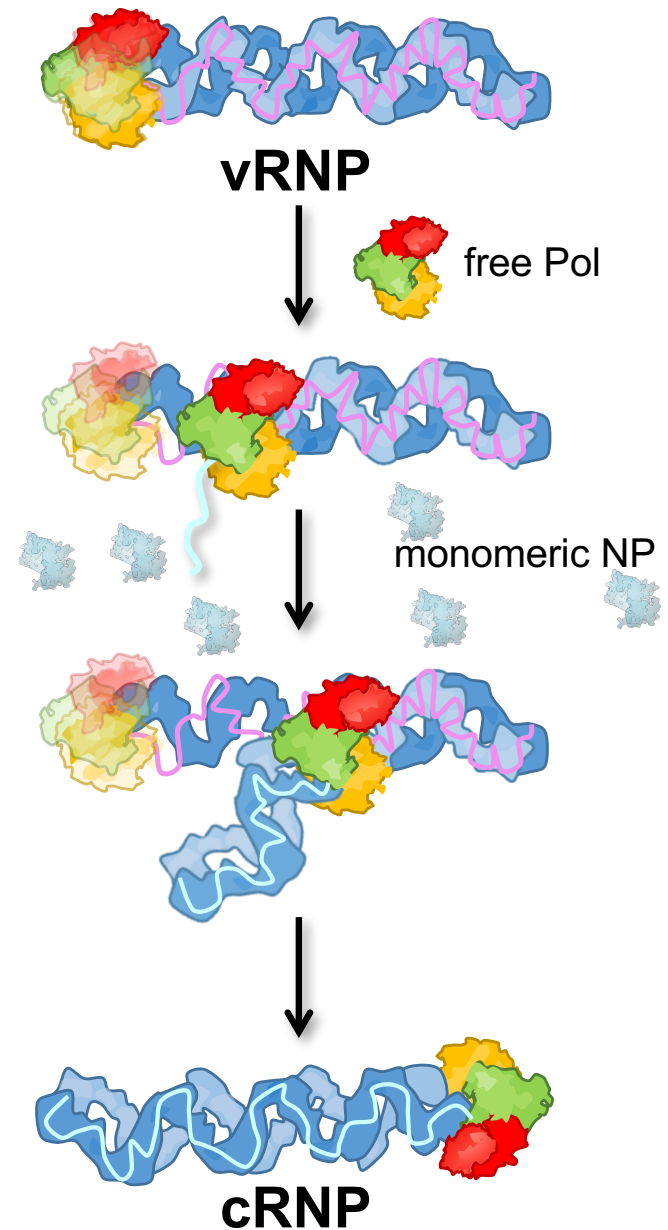


Regulated RNP assembly

Transcription (cap snatching)



Replication

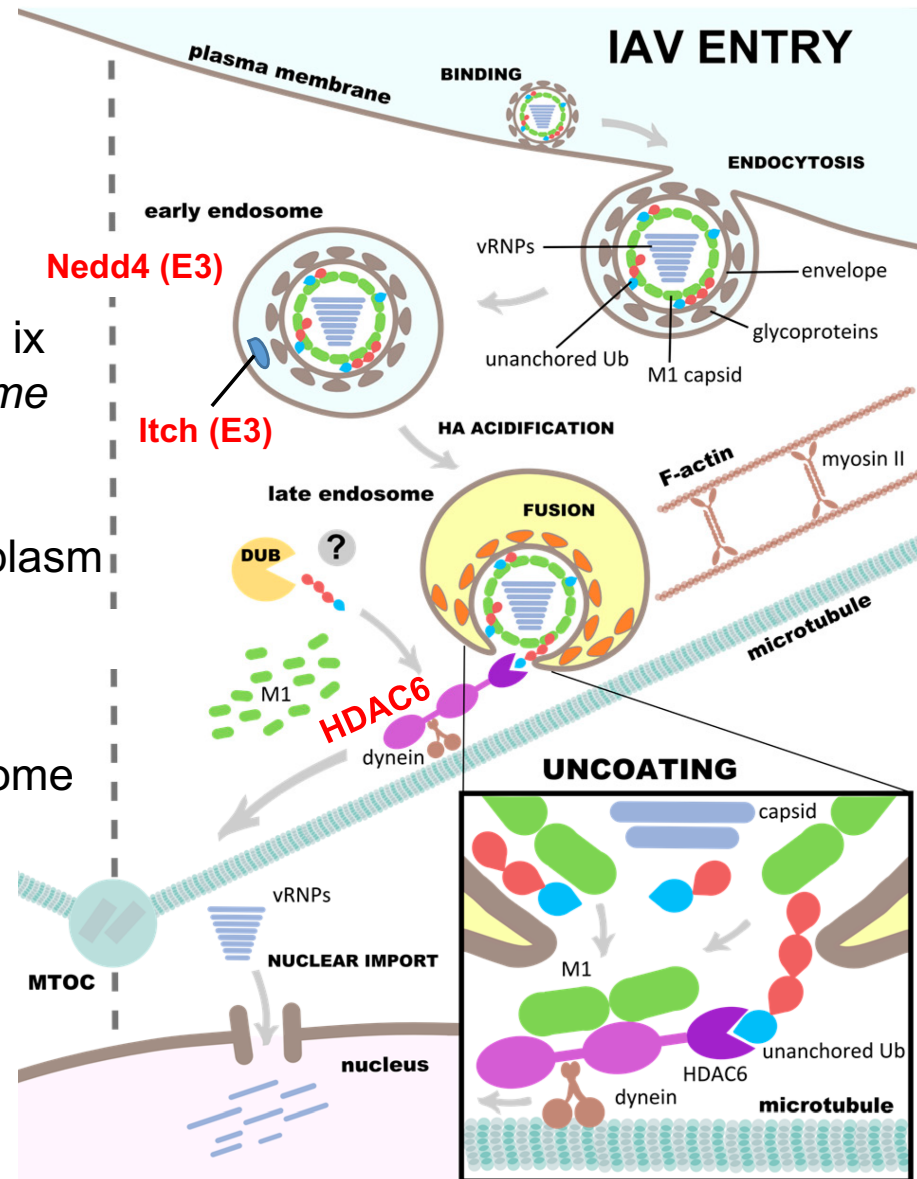


Getting into nucleus: ubiquitin, Itch and HDAC6 facilitate uncoating

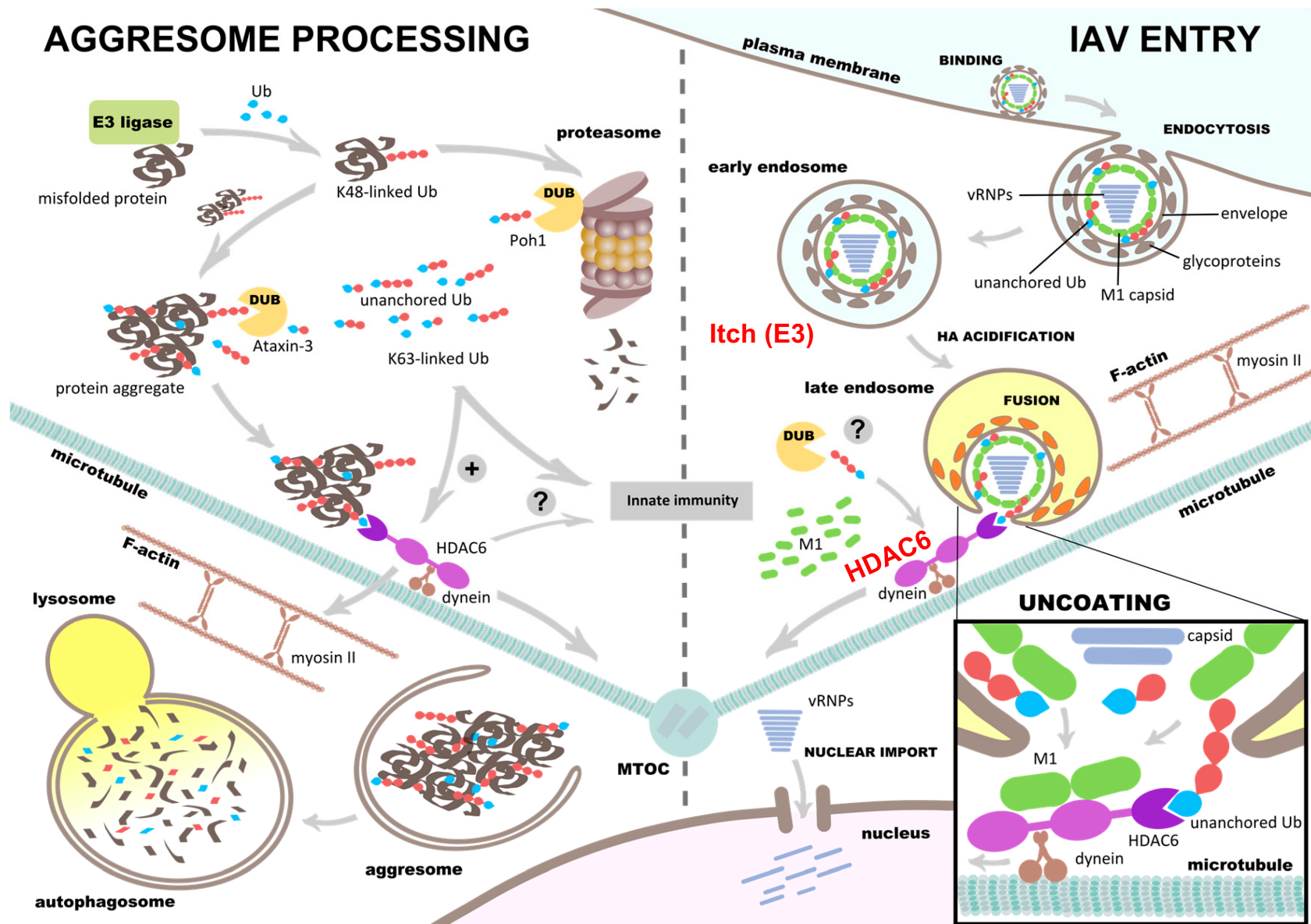
Nedd4 – E3 Ub ligase
targets IFITM3
enables release from endosome

Itch – E3 Ub ligase
recruited inside endosome during ix
helps release virion from endosome
targets M1

HDAC6 – histone deacetylase, also in cytoplasm
deacetylates tubulin
key for aggresome formation
binds free/unanchored Ub
directs bound complex to aggresome
promotes virion disassembly



Getting into nucleus: ubiquitin, Itch and HDAC6 facilitate uncoating



Getting into nucleus: importance of importins

Nuclear pore complex (NPC) is gatekeeper
proteins <40kDa can passively enter
larger proteins need **importins**

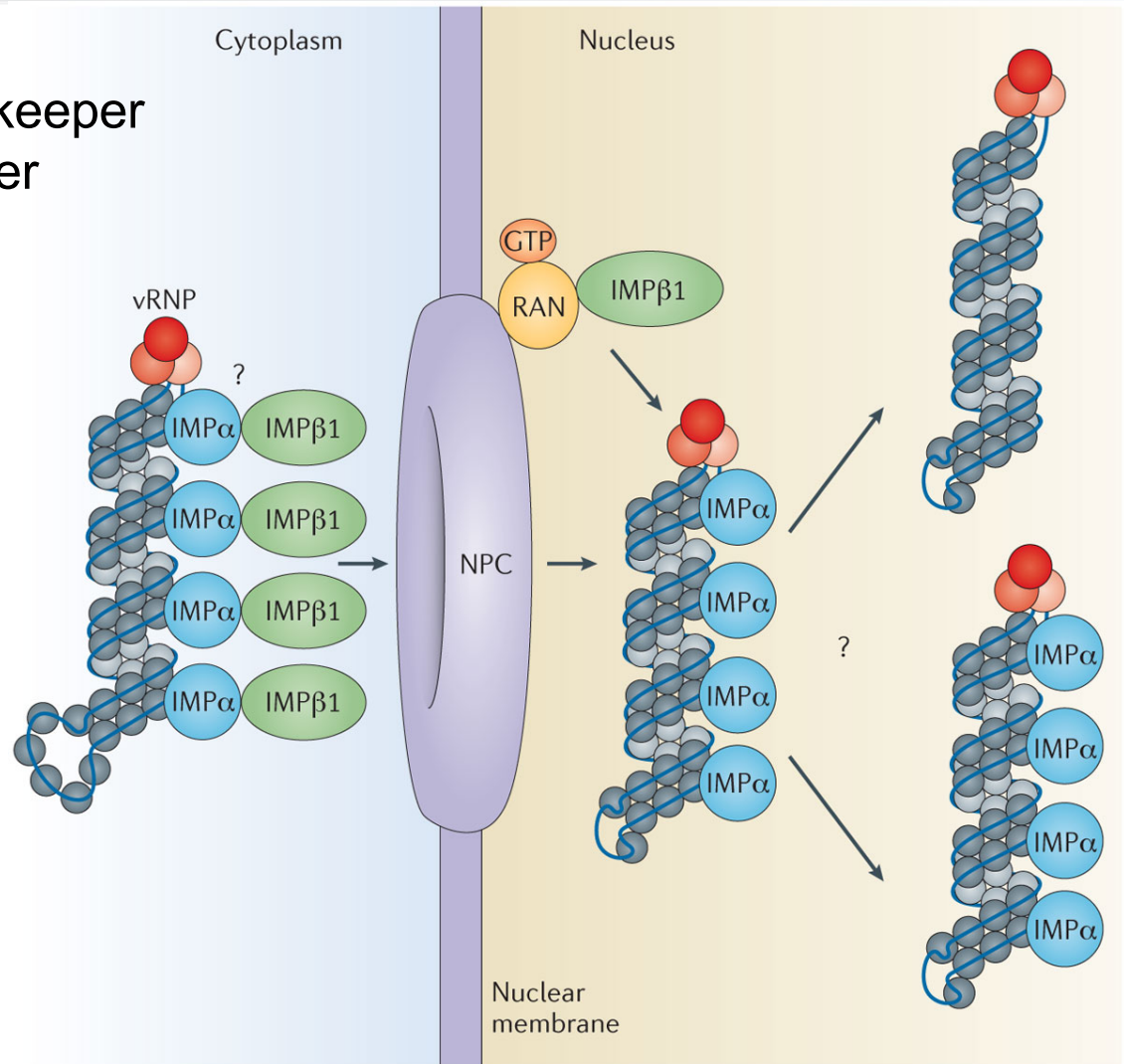
IMP α – adaptor, recognized NLS

IMP β – transport receptor

Cargo:IMP α :IMP β transit NPC

RAN dissociates and exports IMP β

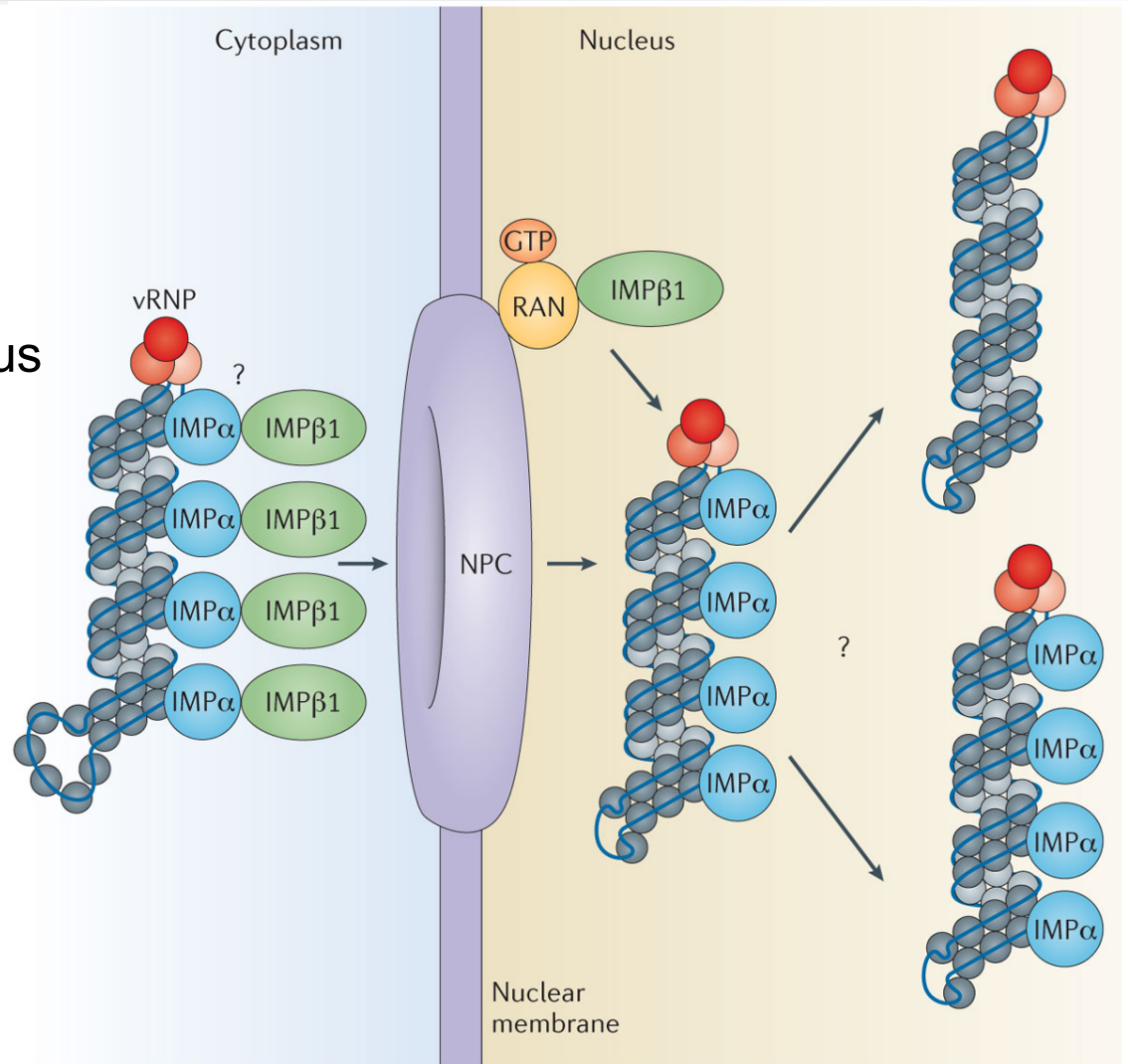
CSE1L dissociate IMP α from cargo



Getting into nucleus: importance of importins

PB2, PB1 and NP have well defined NLS

NP:IMP α 1-IMP β 1 or **NP:IMP α 5-IMP β 1** thought to drive RNP to nucleus



Nature Reviews | Microbiology

Eisfeld, et al. 2014 Nature Reviews Micro

Getting into nucleus: 8-segmented ride sharing?

PB2, PB1 and NP have well defined NLS

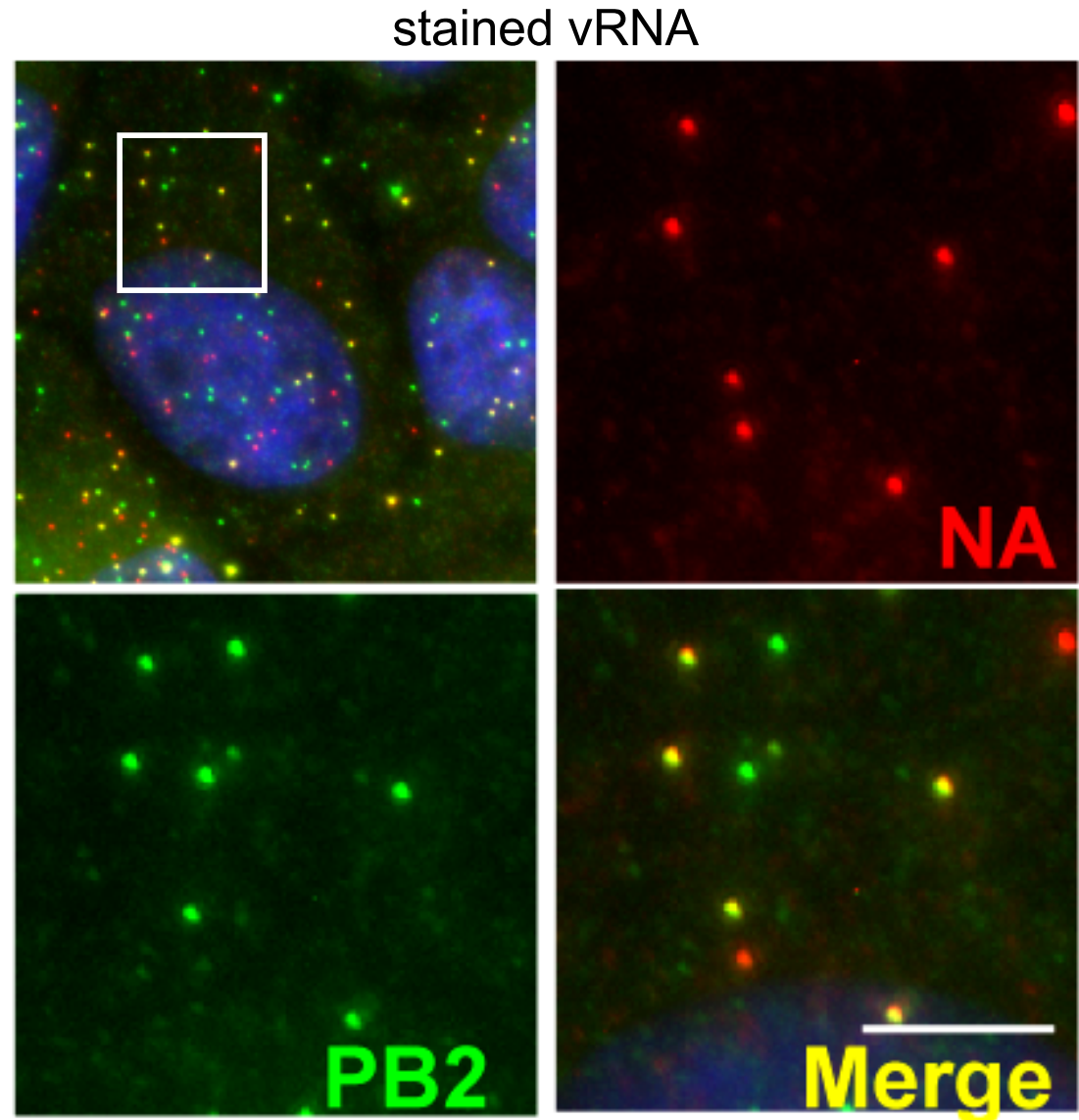
NP:IMP α 1-IMP β 1 or **NP:IMP α 5-IMP β 1** thought to drive RNP to nucleus

smFISH suggests incoming RNPs remain associated during import, and dissociate only after nuclear import (Chou, et al. 2013).

vRNPs replicate as distinct spots in nucleus

in <60m, vRNPs have entered the nucleus, dispersed and begun transcribing and replicating

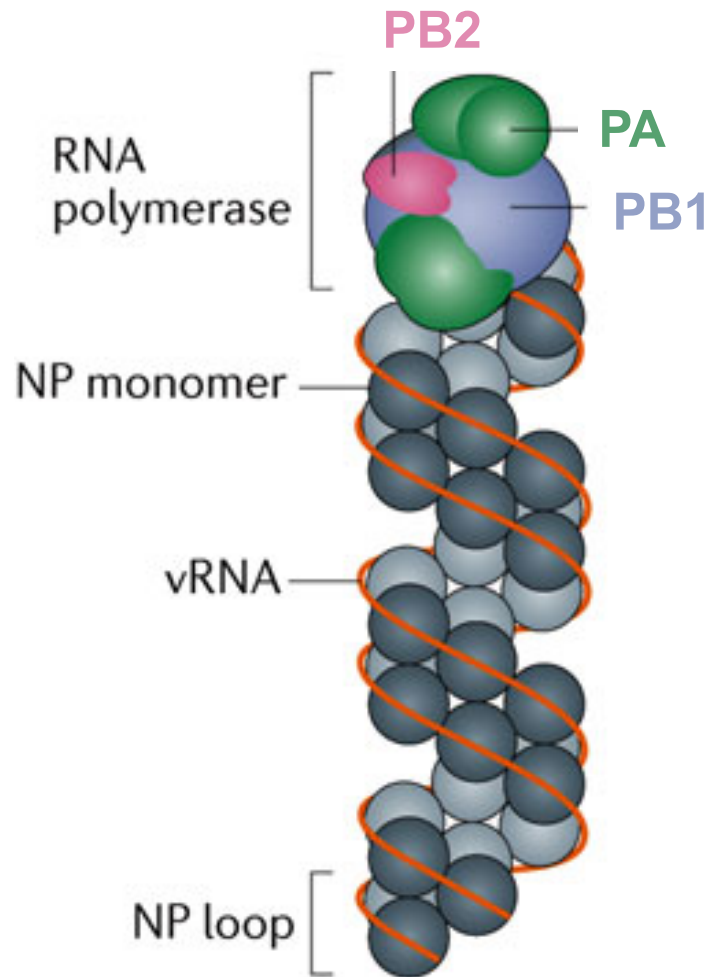
1/3-1/2 of virions fail to exit endosome



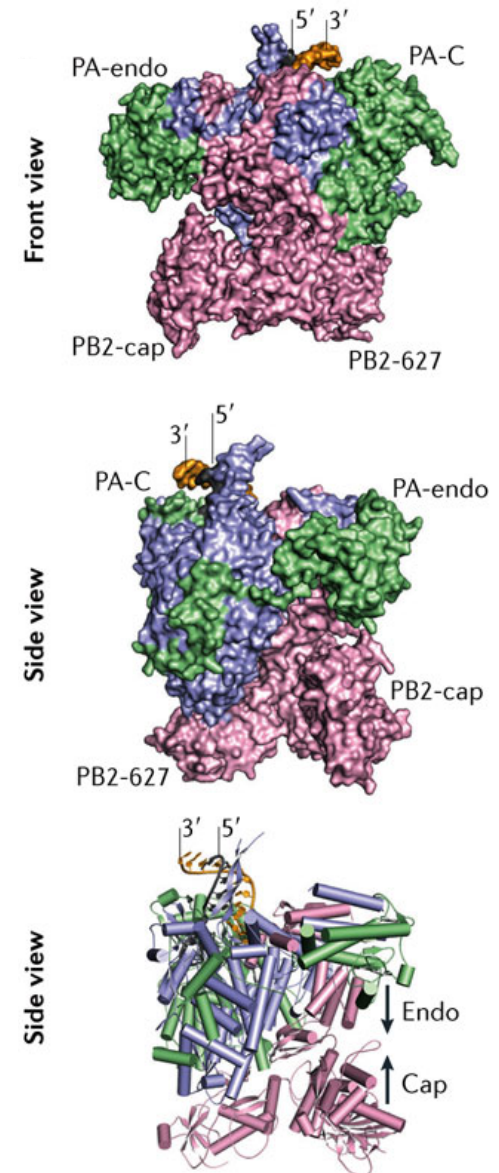
20m post-infection

Chou, et al. 2013 PLoS Pth

Conformational control of polymerase function

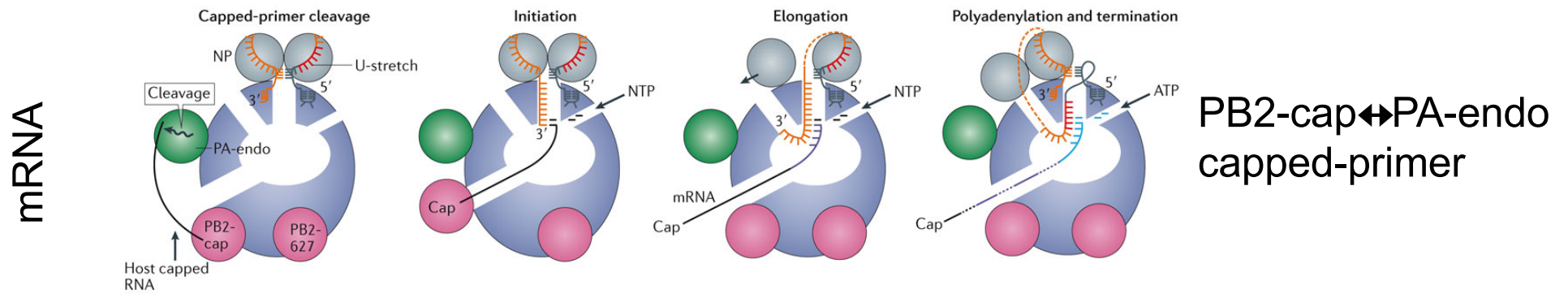


b Influenza A virus bound to vRNA

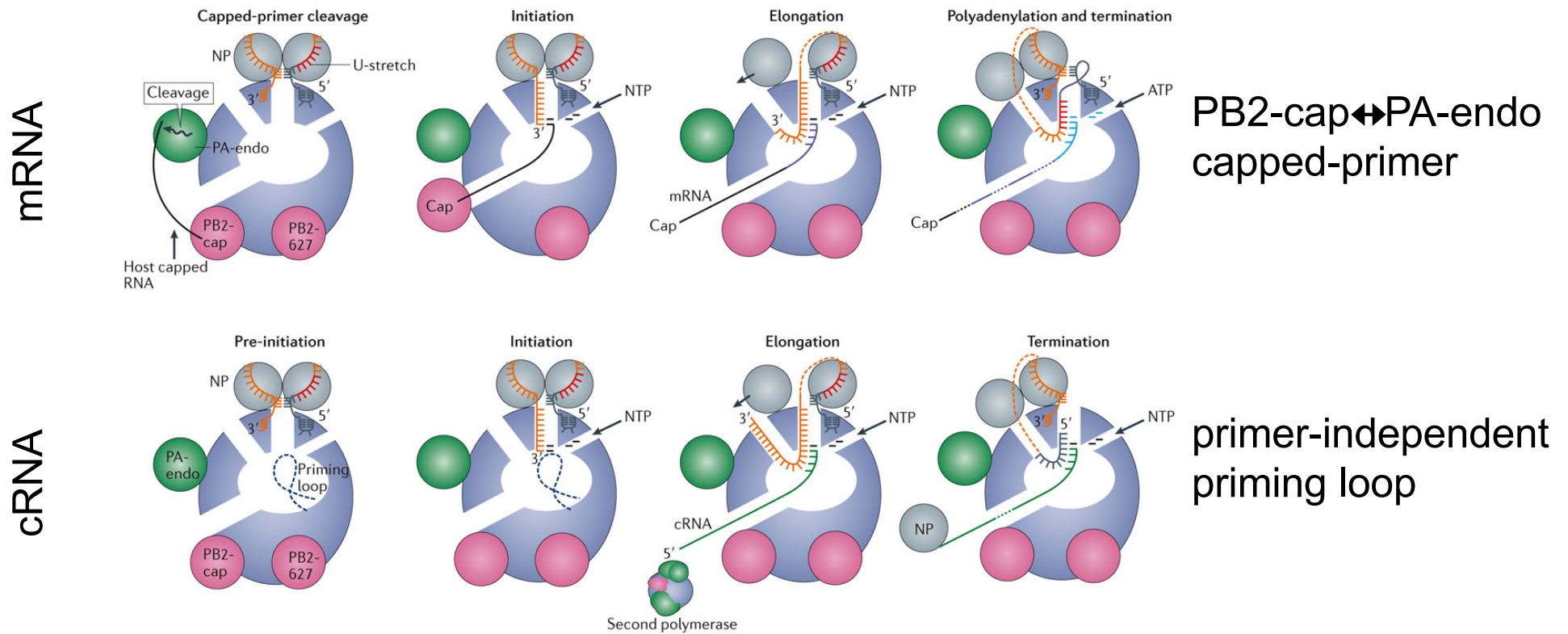


Te Velthuis & Fodor 2016
doi:10.1038/nrmicro.2016.87

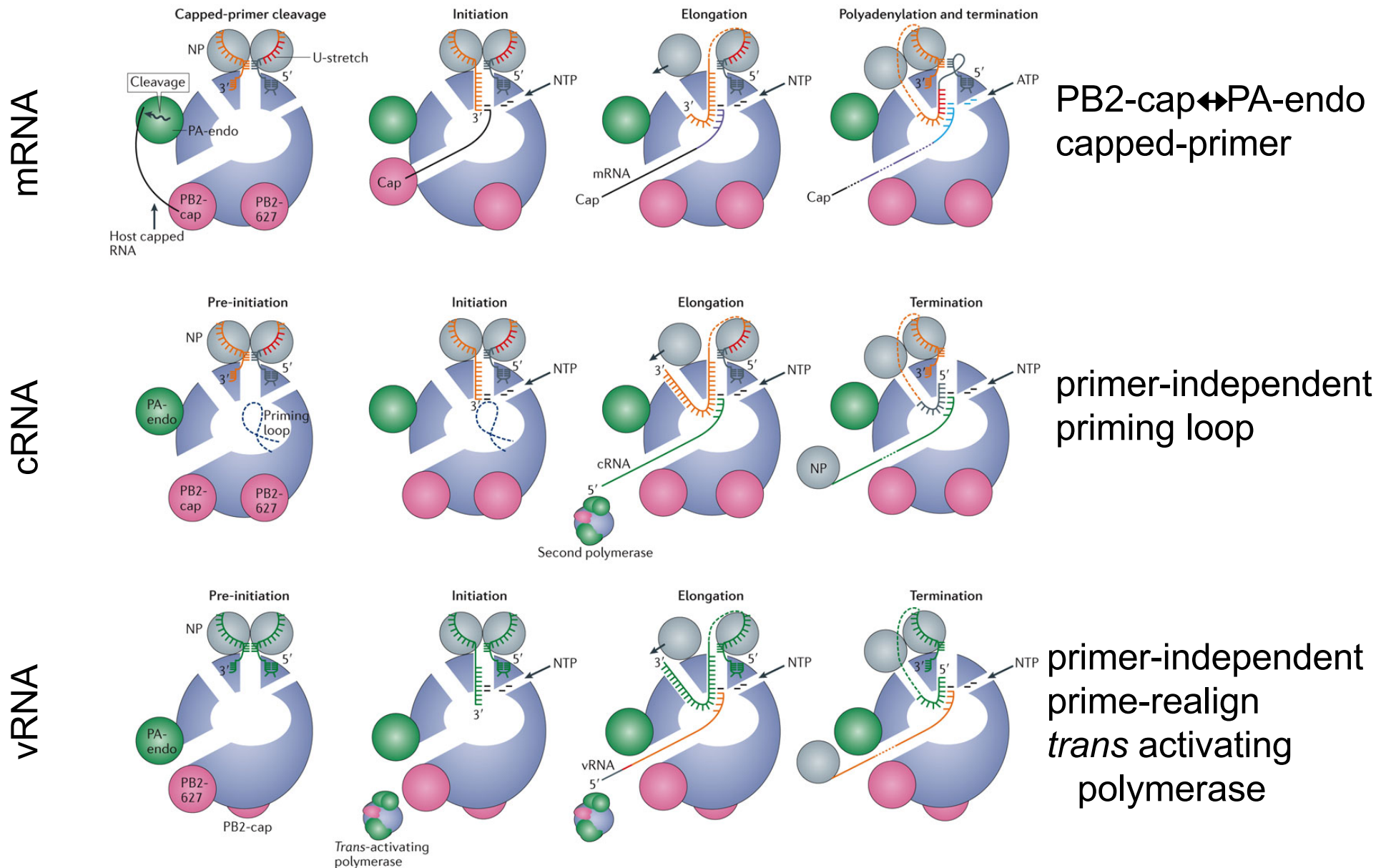
Conformational control of polymerase function



Conformational control of polymerase function



Conformational control of polymerase function



Cap-snatching co-factors

DNA-dependent DNA polymerase II (pol II) performs transcription of host genes

Influenza polymerase binds host pol II via pol II C-terminal domain (CTD), which encodes up to 52 repeats of YS₂PTS₅PS.

pS5 indicative of initiating pol II.

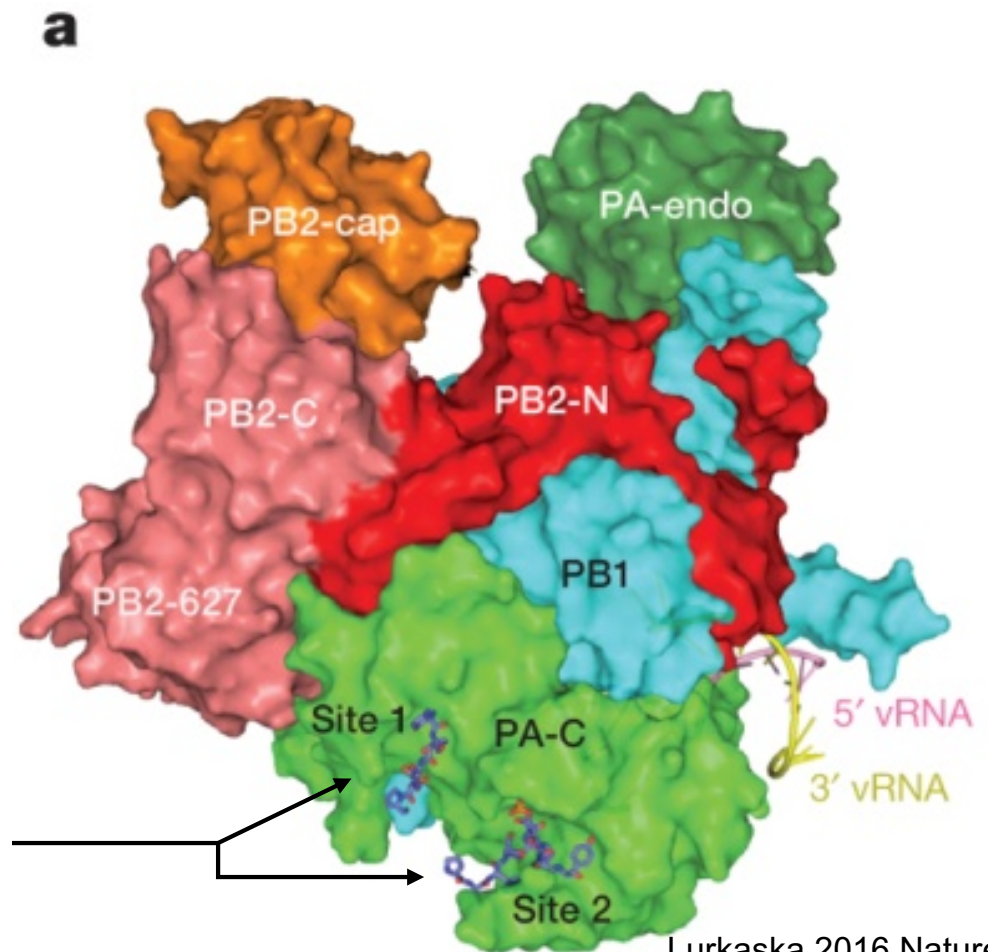
pS2 indicative of elongating pol II.

Influenza pol steals caps from diverse host transcripts, including snRNA, snoRNA, short promoter-associated transcripts (rarely pre-mRNA or mRNA)

Host pol II degraded during infection

Flu pol also binds pol II modulators, e.g. hCLE

PA specifically binds pS5-CTD



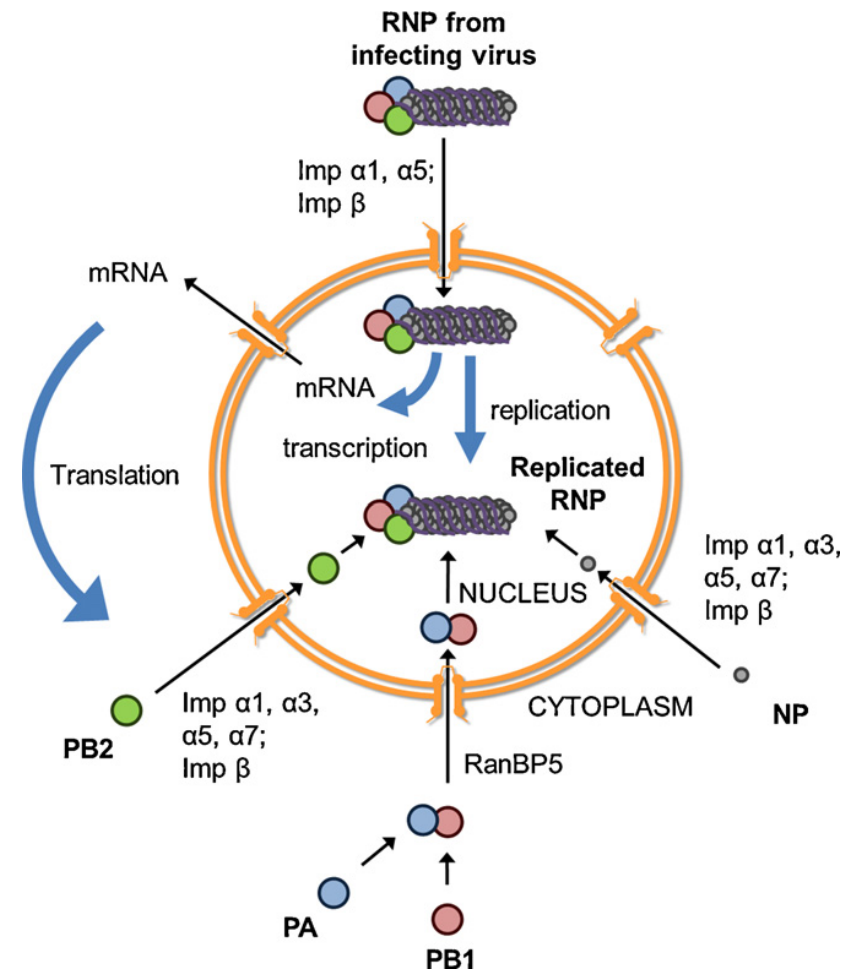
Nuclear import and assembly of polymerase and NP

PB2 and **NP**– Which $\text{IMP}\alpha$ is used?
Redundant?

PB1 and **PA** both have NLS, but import is inefficient. Imported by RanBP5 as dimer.

RanBP5 ($\text{IMP}\beta 3$) – non-classical import factor, directly engages NPC

RanBP5 binds PB1:PA, but not trimer \rightarrow prevent premature polymerase formation?



Hutchinson & Fodor 2012 Vaccine

Chaperones:

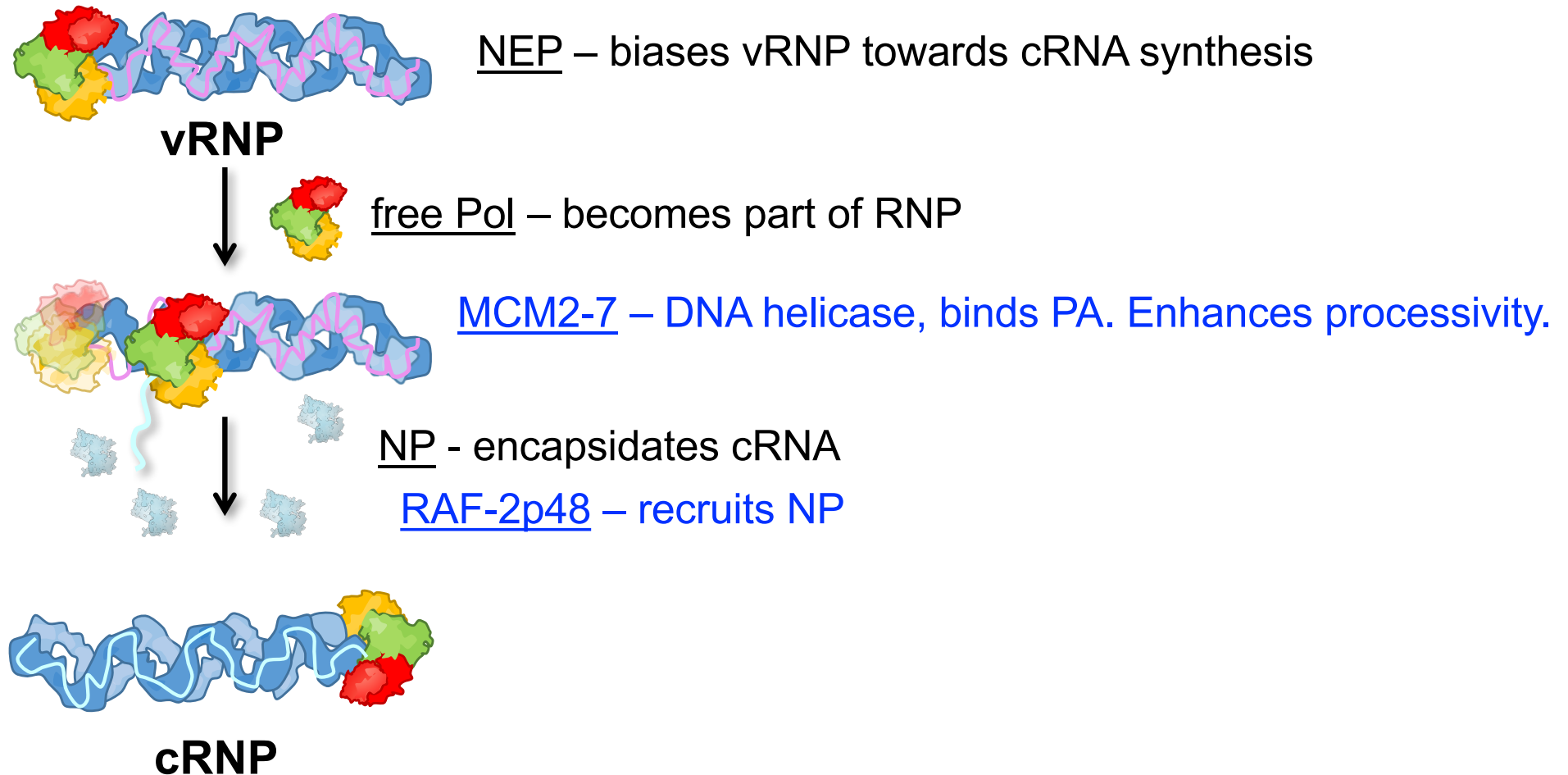
CCT complex binds PB2 in cytoplasm – aids folding?

Hsp90 binds PB2 – relocalized to nucleus – assembles PB2 onto pre-formed PB1:PA

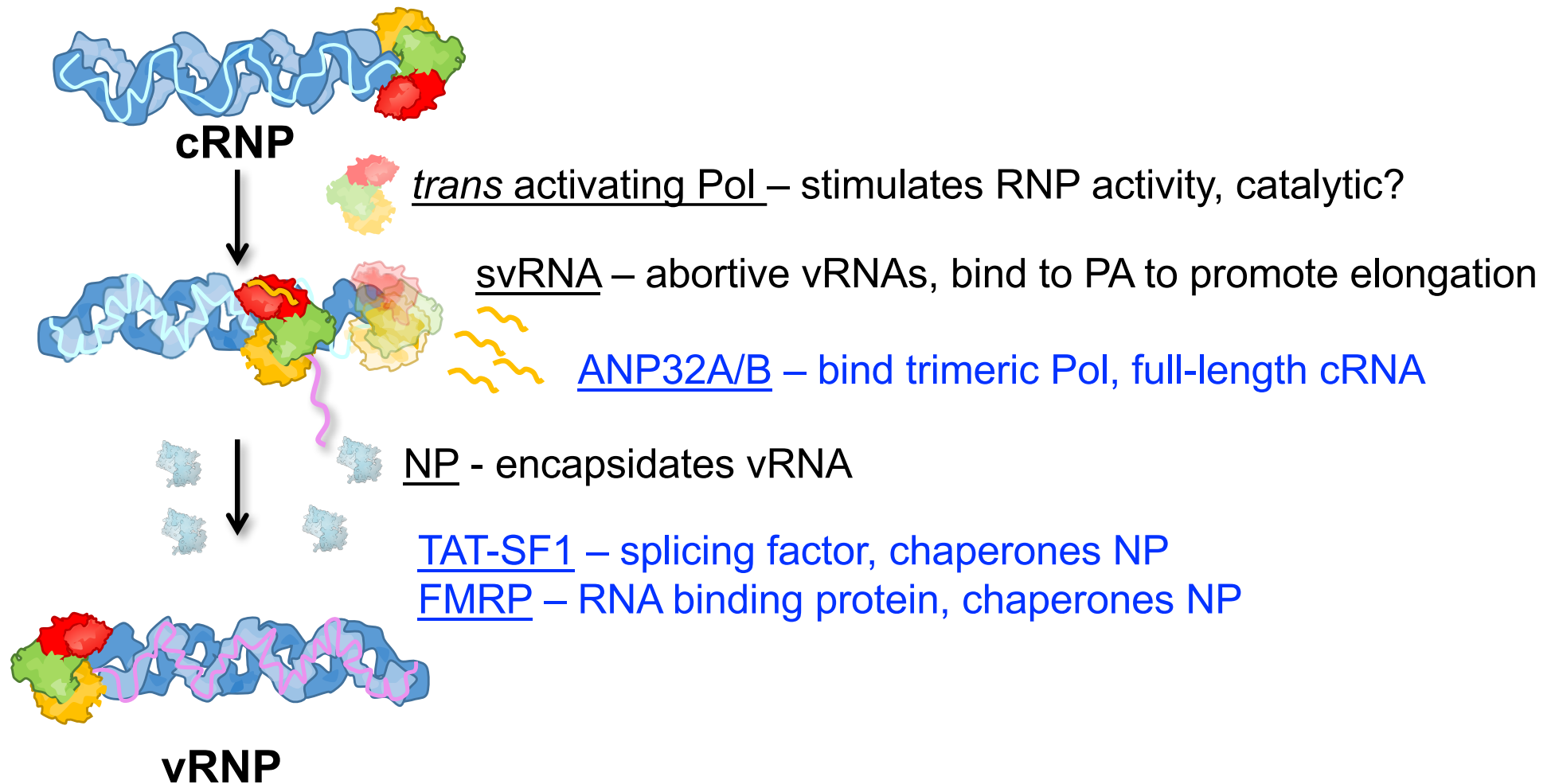
Others – Hsp90 co-chaperone p23, Hsp60, Hsp70 implicated, but not defined

$\text{IMP}\alpha$ – suggest role post-import to stabilize assembly intermediates

Factors directing vRNA → cRNA synthesis



Factors directing cRNA → vRNA synthesis



Genome replication and RNP assembly

Many large questions remain:

What is the role of trans polymerase?

What drives conformational changes in the polymerase?

Are there polymerases dedicated to just m-, c- or vRNA synthesis?

Why doesn't recombination/copy-choice occur?

How is NP loaded, and where?

vRNP export

The “daisy chain” model

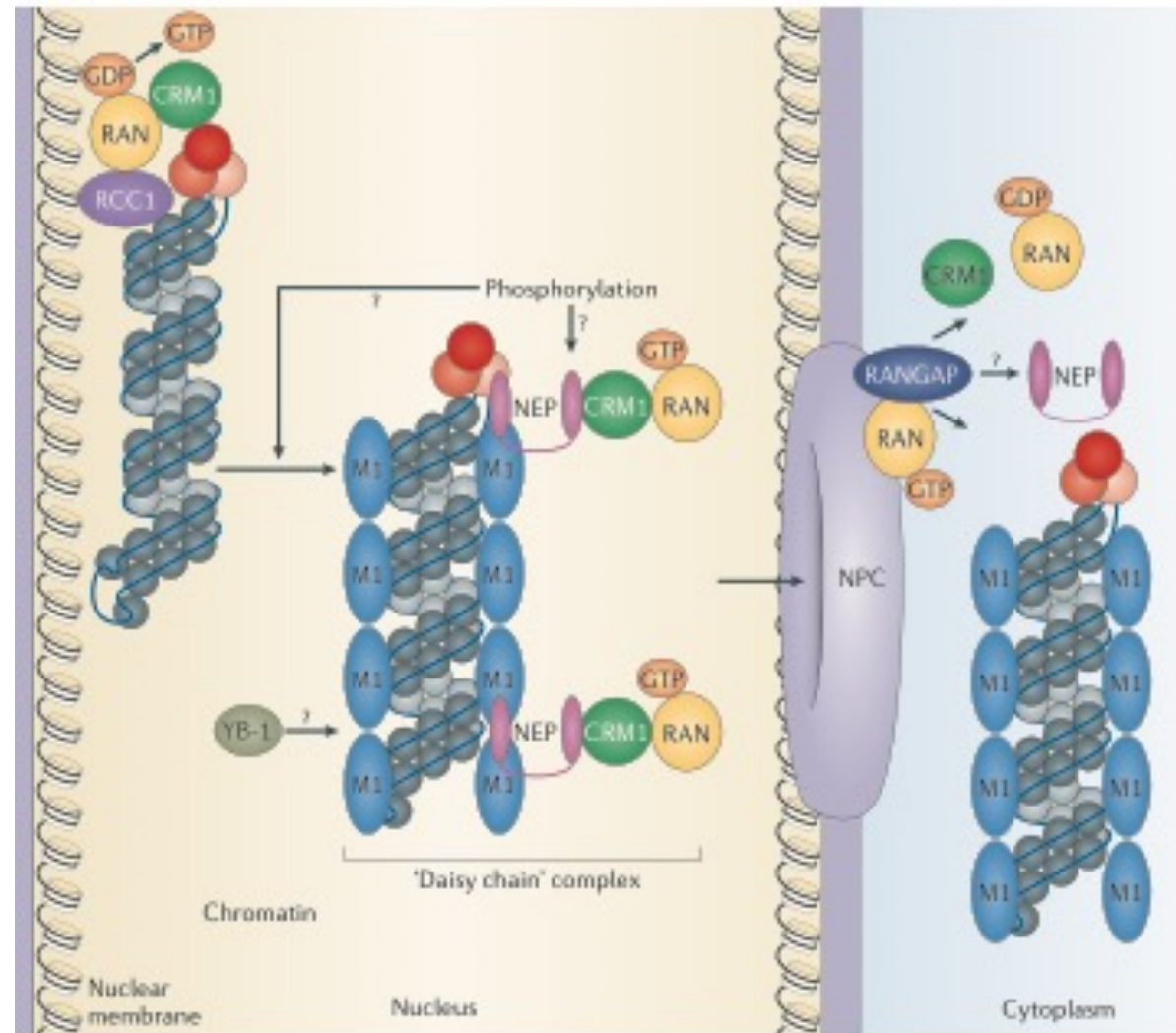
M1 binds to NP in RNP
NEP binds to M1
Crm1/RanGTP binds NEP
(NEP has 2 NES)
export via NPC

Crm1 is an importin β
relies on RanGTP
Rcc1, a GEF for Crm1
tethered to chromatin

RNPs also co-localize to chromatin

vRNP are not re-imported
bound M1 blocks RNP NLS

Timing of export thought to be dictated
by slow accumulation of NEP – inefficient splicing
as a built in “molecular timer” (Chua, 2013)



vRNP trafficking

vRNPs are 2.5-6 MDa in size

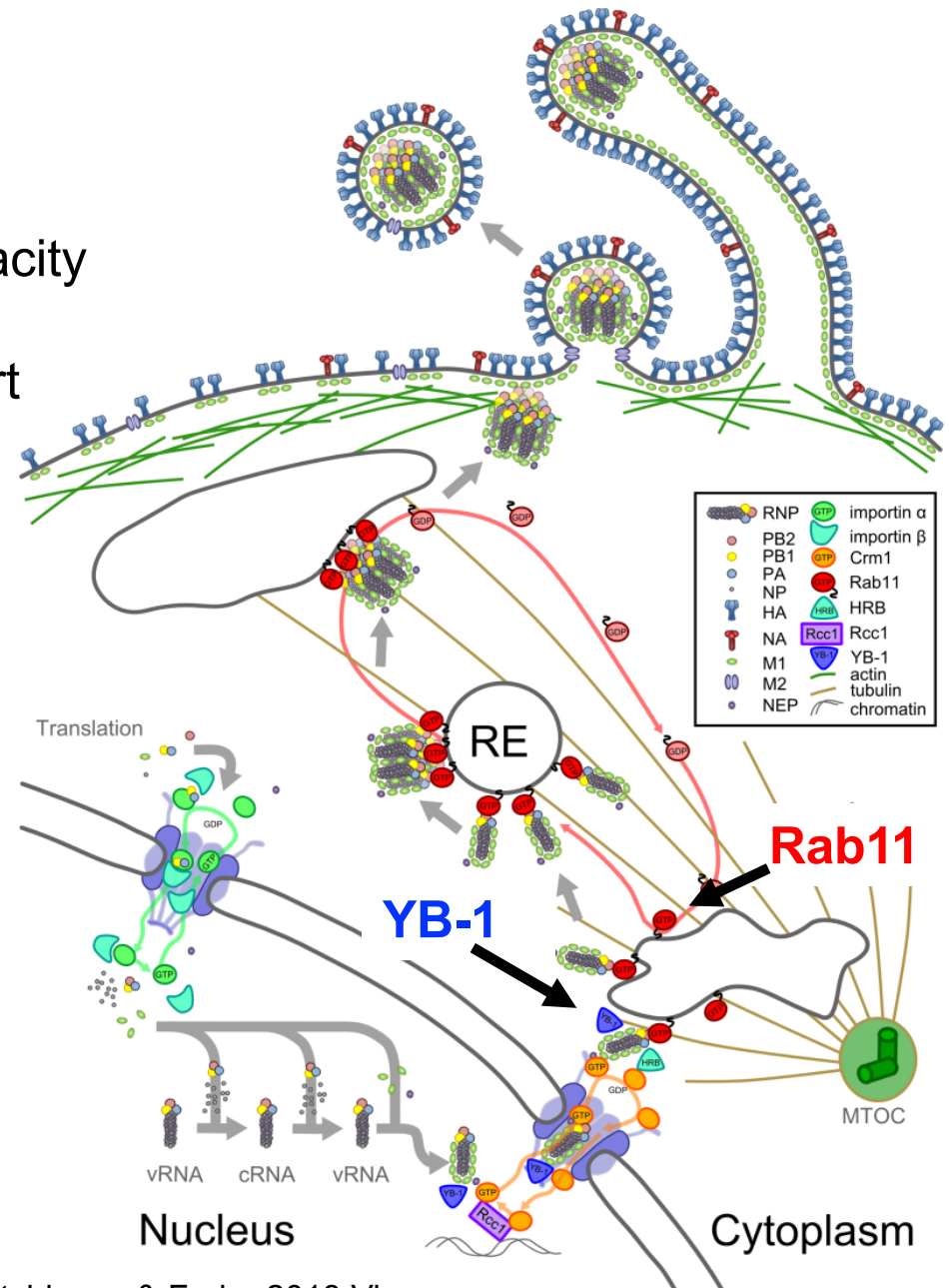
- virally induced apoptosis activates caspase which cleave Nup153 in NPC
- cleaved Nup153 has larger export capacity

YB-1 (Y-box binding protein 1) aids export

- binds RNP during export
- helps direct RNP to microtubules and MTOC once in cytoplasm

exported vRNPs associate with Rab11-positive recycling endosomes

RNPs/RE trafficked to apical plasma membrane vis microtubules



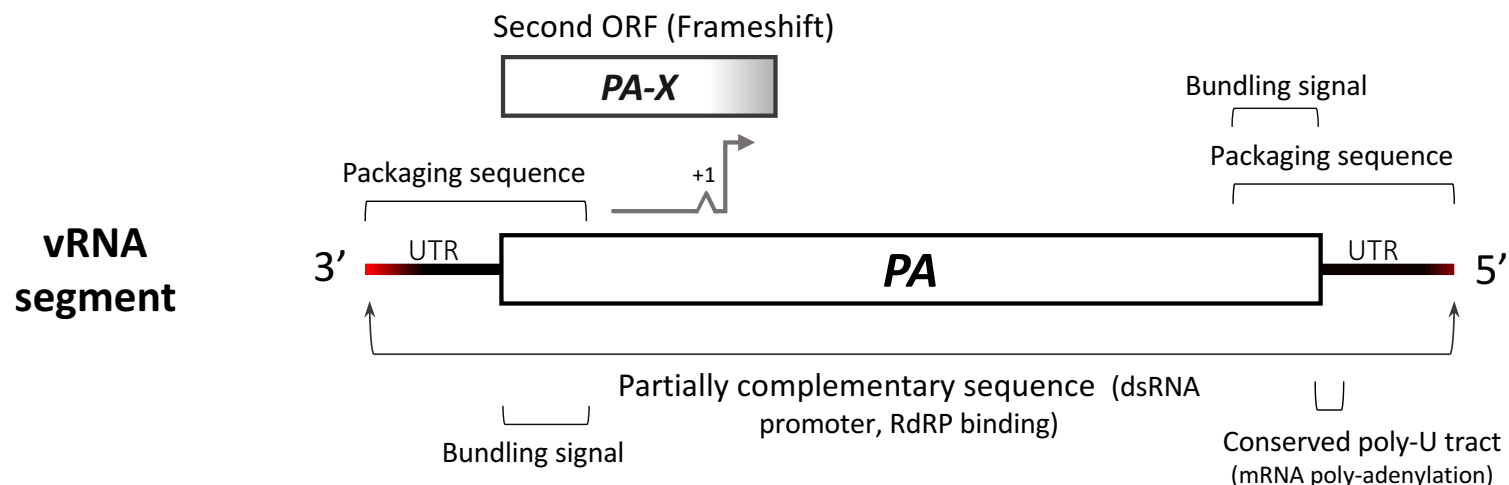
How can you study polymerase, NP or RNP movement in real time during infection? A reporter virus.

Benefits:

- Real-time, longitudinal, quantitative measure of replication
- Non-invasive and serial assessment of viral load, tissue tropism, transmission

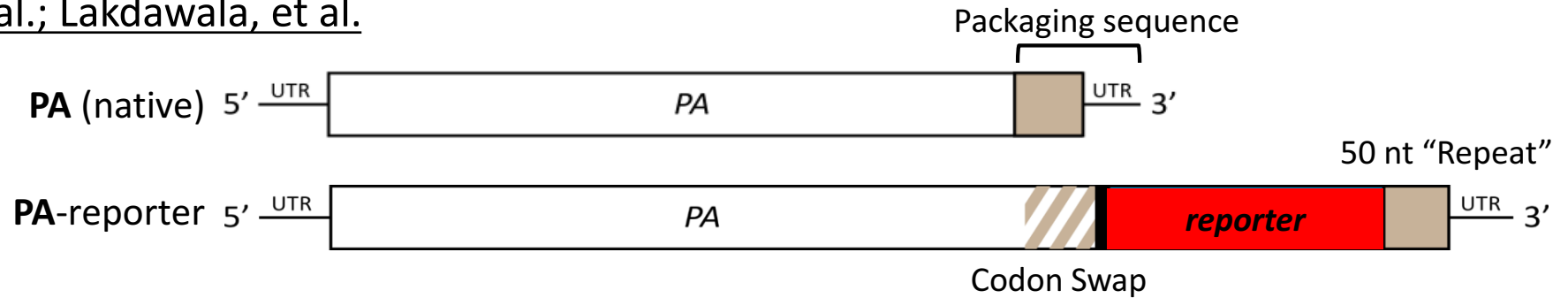
Challenges:

- Segmented genome
- All of the viral genes are critical *in vivo*
- Complex genome architecture
- Does not tolerate large insertions
- Insertions attenuate replication



Influenza reporter viruses

Tran, et al.; Lakdawala, et al.



- Fusion to C-term of polymerase subunit
- Restoration of packaging signals by repeating 50 nt of PA ORF
- Codon swap increases stability

Avilov, et al. – PB2

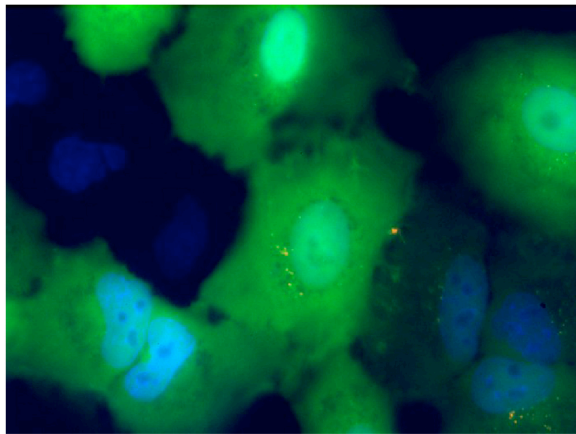


- Fusion to very small GFP11 to C-term of polymerase subunit
- GFP11 is a single beta sheet taken from GFP. Not fluorescent on its own
- PB2-GFP11 reconstitutes GFP in cells expressing GFP 1-10

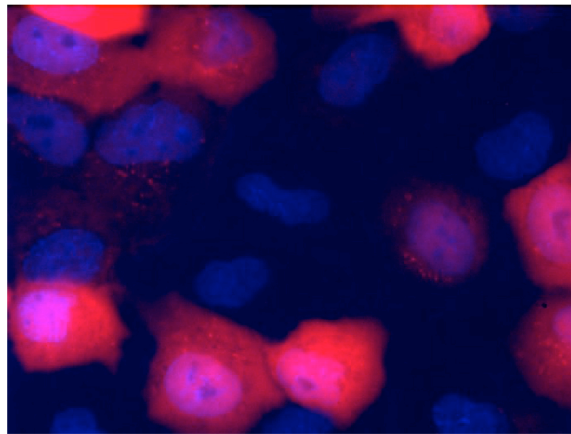
Detecting co-infection with PA-fusion viruses



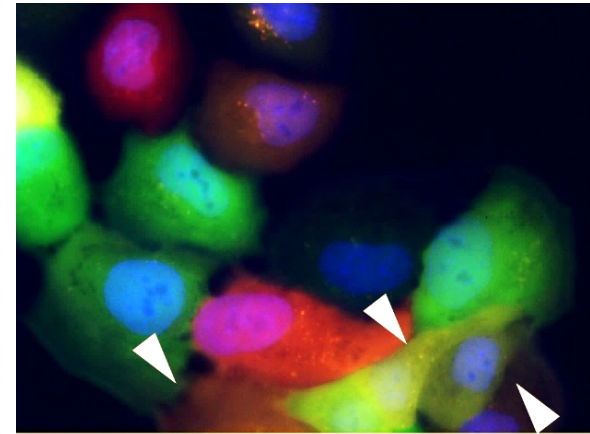
Virus: GFP



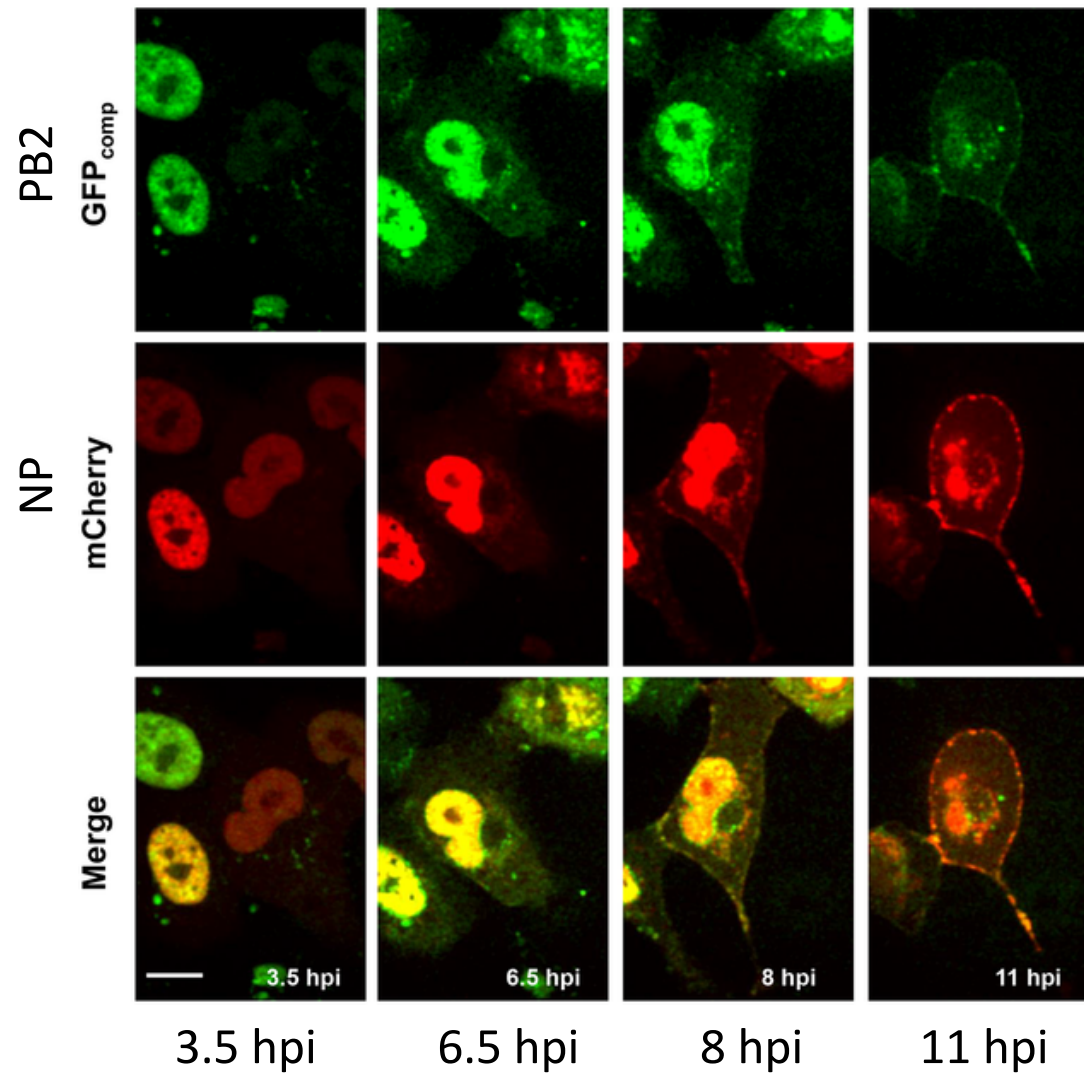
RFP



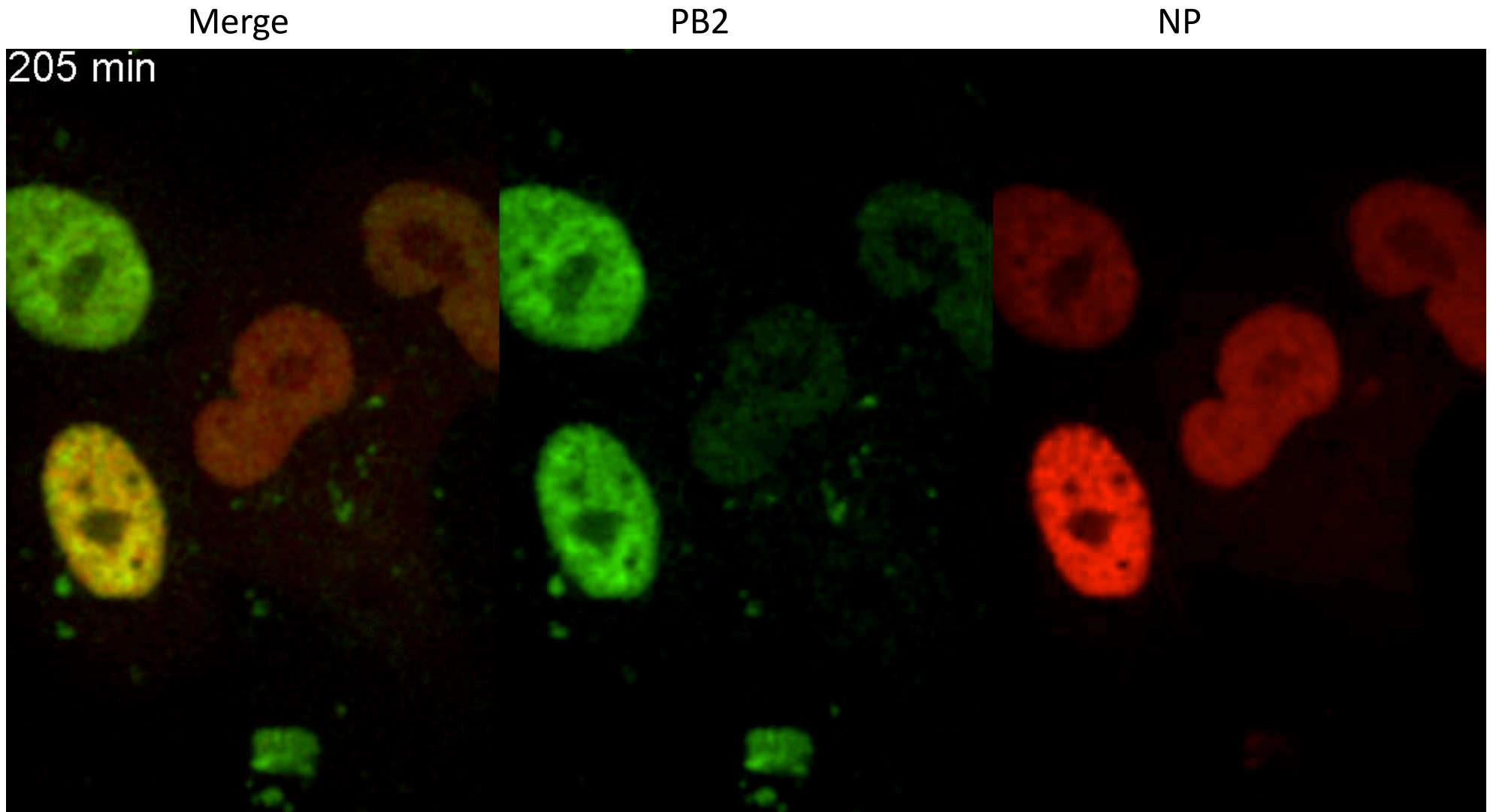
GFP+RFP



Tracking RNP export with PB2-GFP11 and NP-mCherry

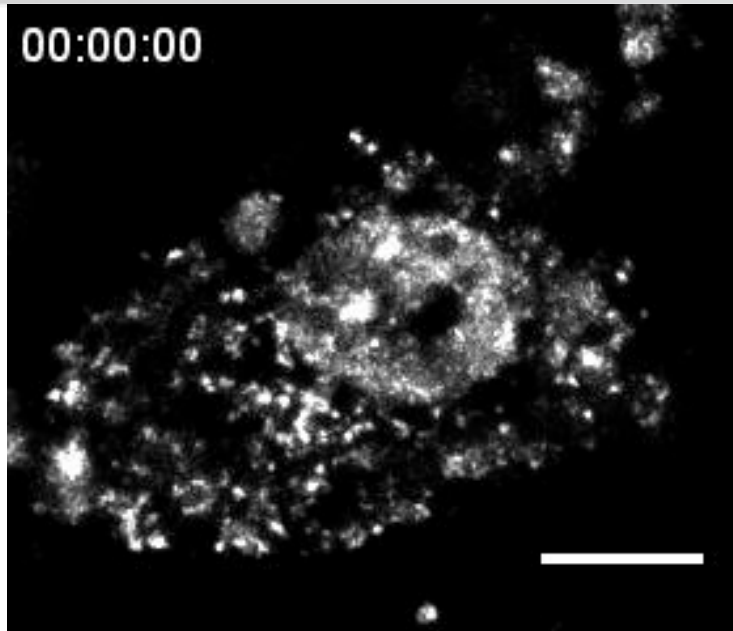


Tracking RNP export with PB2-GFP11 and NP-RFP



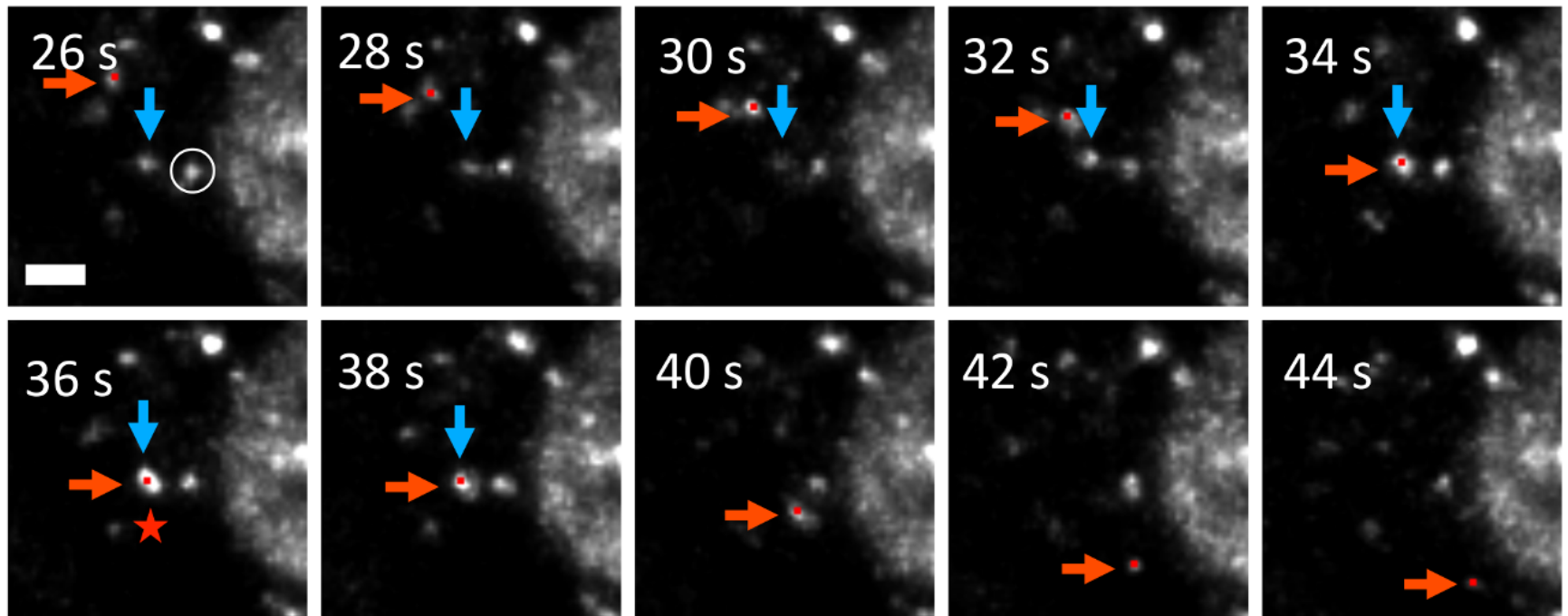
Vero cells

Tracking export with PA-GFP suggests RNPs bundle in cytoplasm



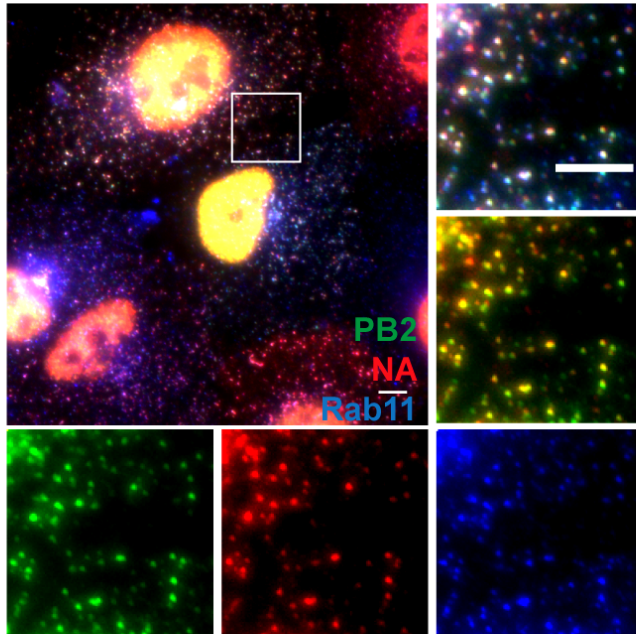
MDCK cells

distinct vRNPs assemble in cytoplasm



vRNPs form “super assemblies” of different genome segments on Rab11 vesicles in cytoplasm

8 hpi

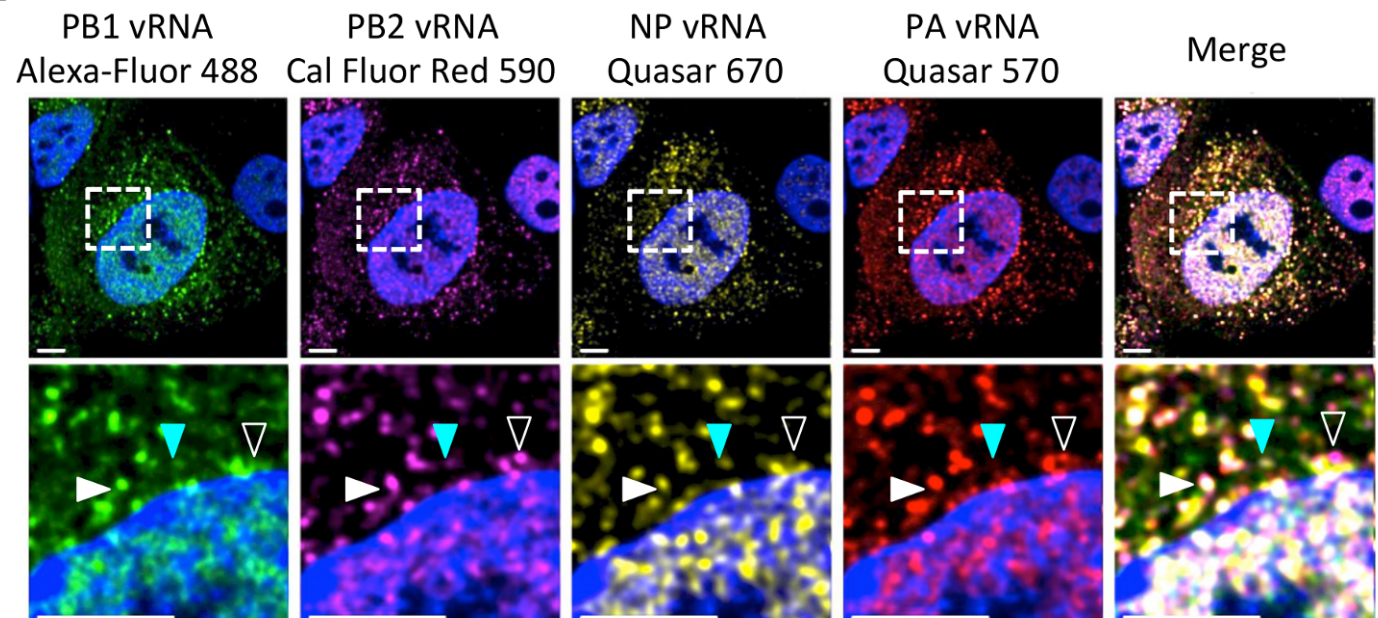


Unknowns:

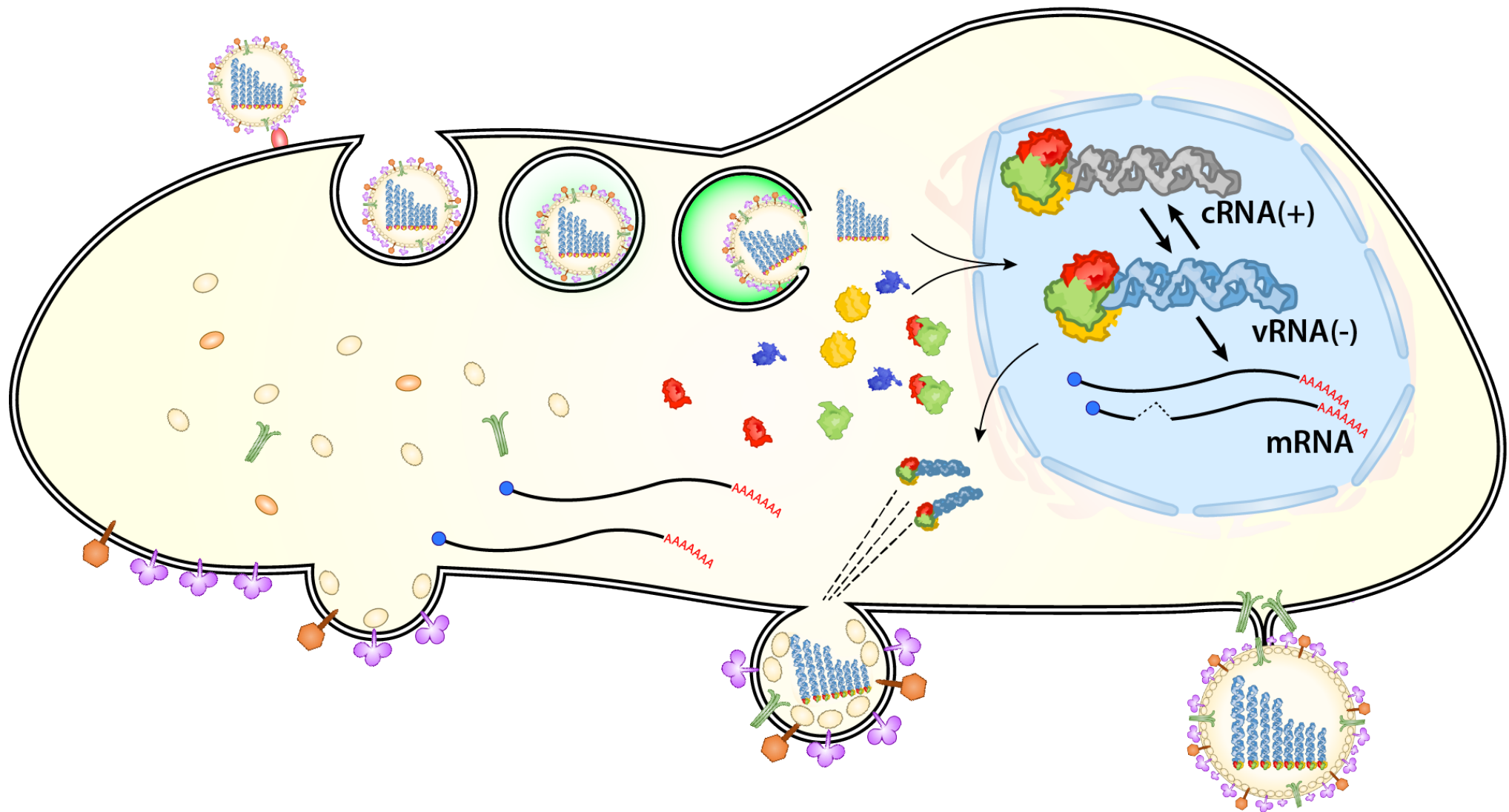
- how and where do vRNPs interact? bundling signals?
- how do virions get 8 distinct vRNPs?
- where does reassortment occur?
- when can reassortment occur? As long as infections occur within ~3hr of each other (Dou 2017 Cell Reports)
- how do RNPs go from RE to plasma membrane?
- do RNPs initiate budding?

vPB2 vNA Rab11

co-localization
of export RNPs



The influenza virus replication cycle



Can cellular co-factors control influenza virus species tropism?

Cross-species transmission of influenza

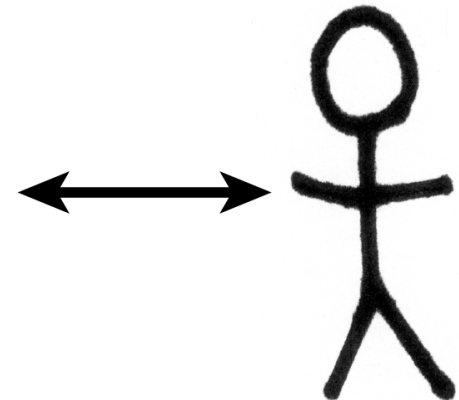
Reservoir



Mixing
Vessel



Terminal
Host

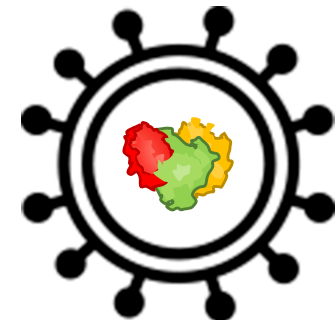
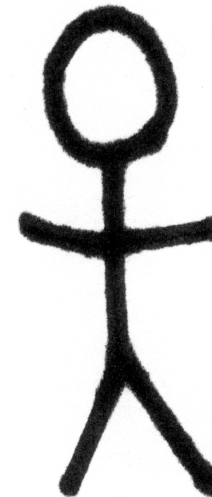
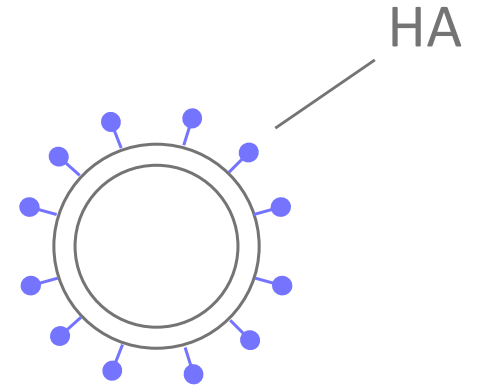
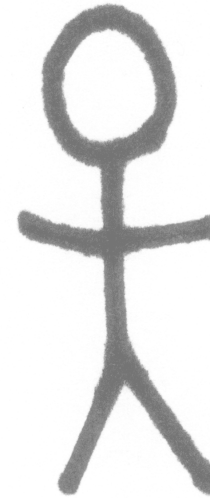


Two predominant blocks to cross-species transmission



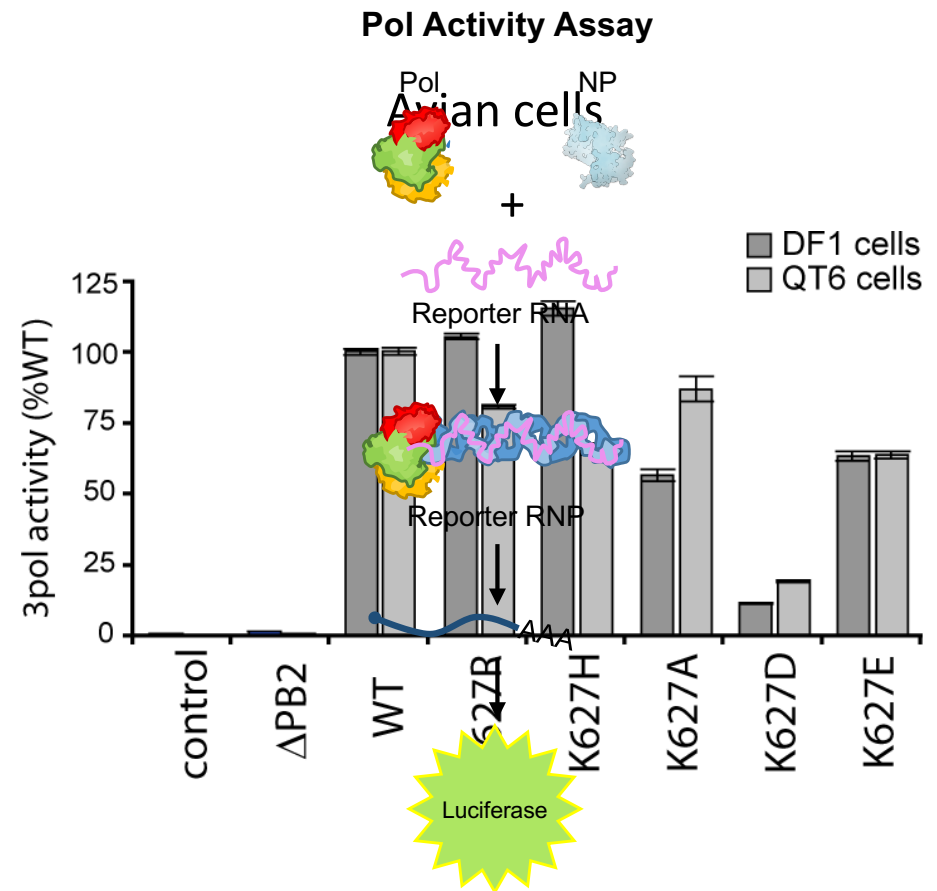
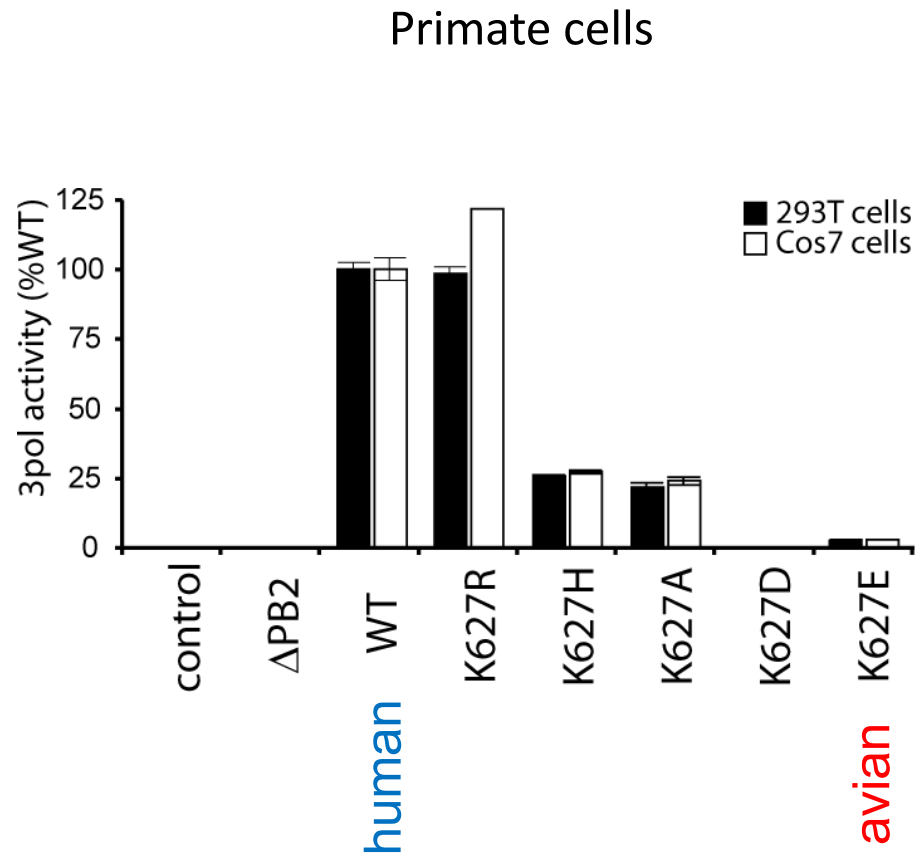
Viral attachment/entry

Viral polymerase



avian polymerases function poorly in humans

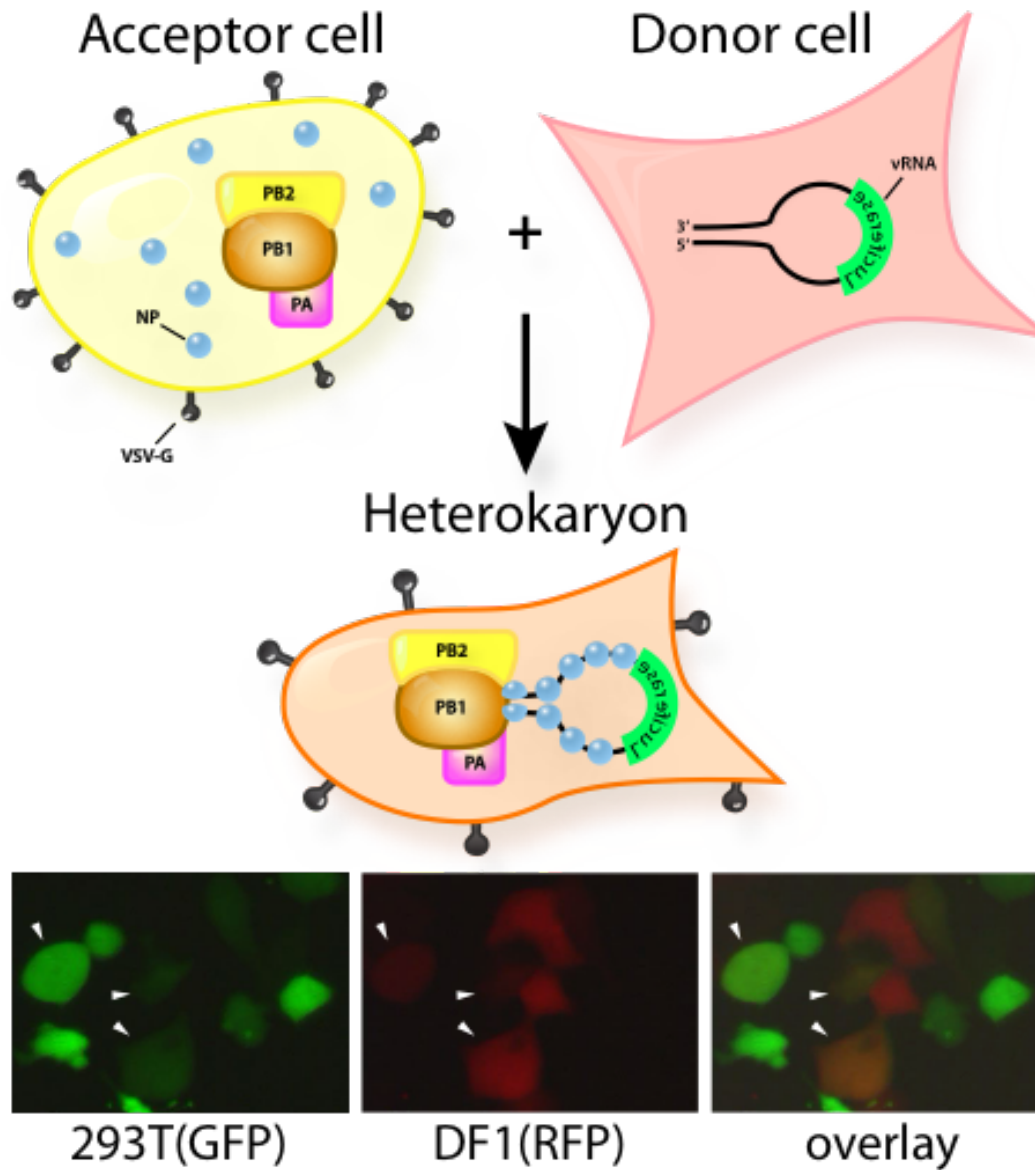
PB2 aa627 regulates polymerase activity in human cells



Subbarao 1993
Mehle 2008
Labadie 2007

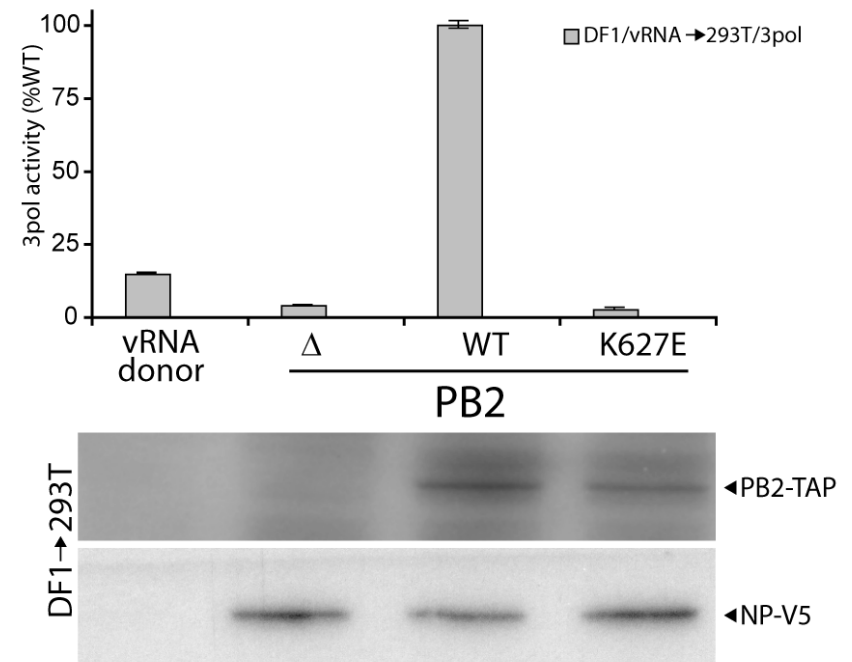
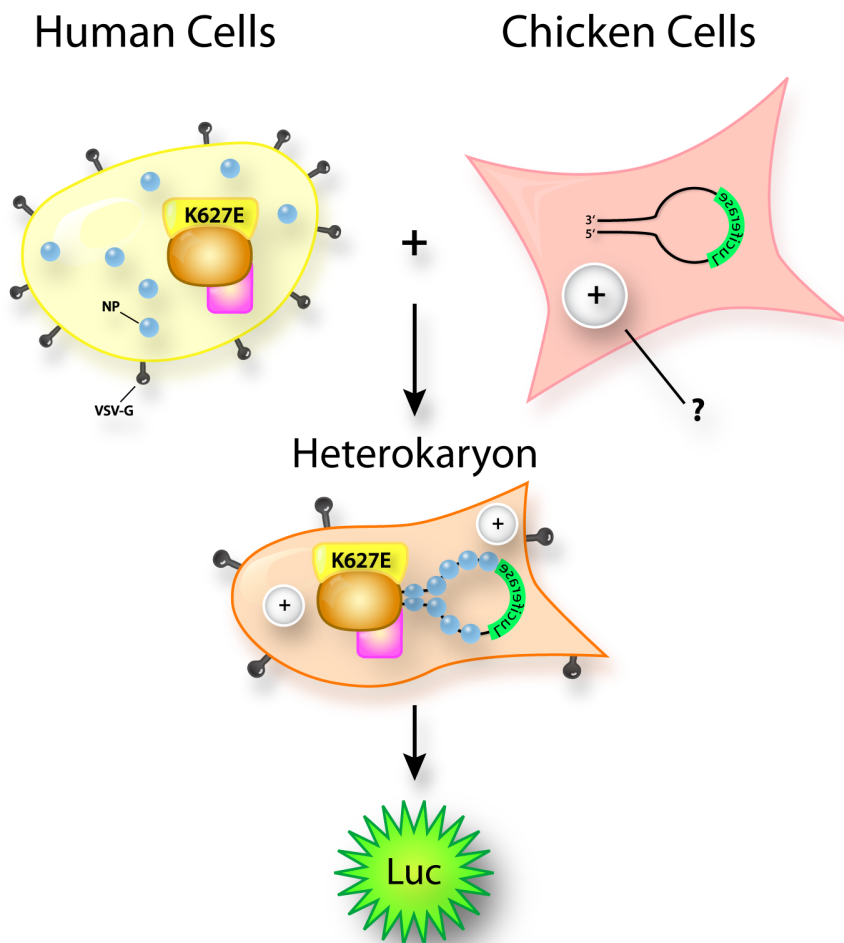
restricted polymerases fail to assembly RNPs

Heterokaryon Assay



Avian cells do not contain a compensatory factor

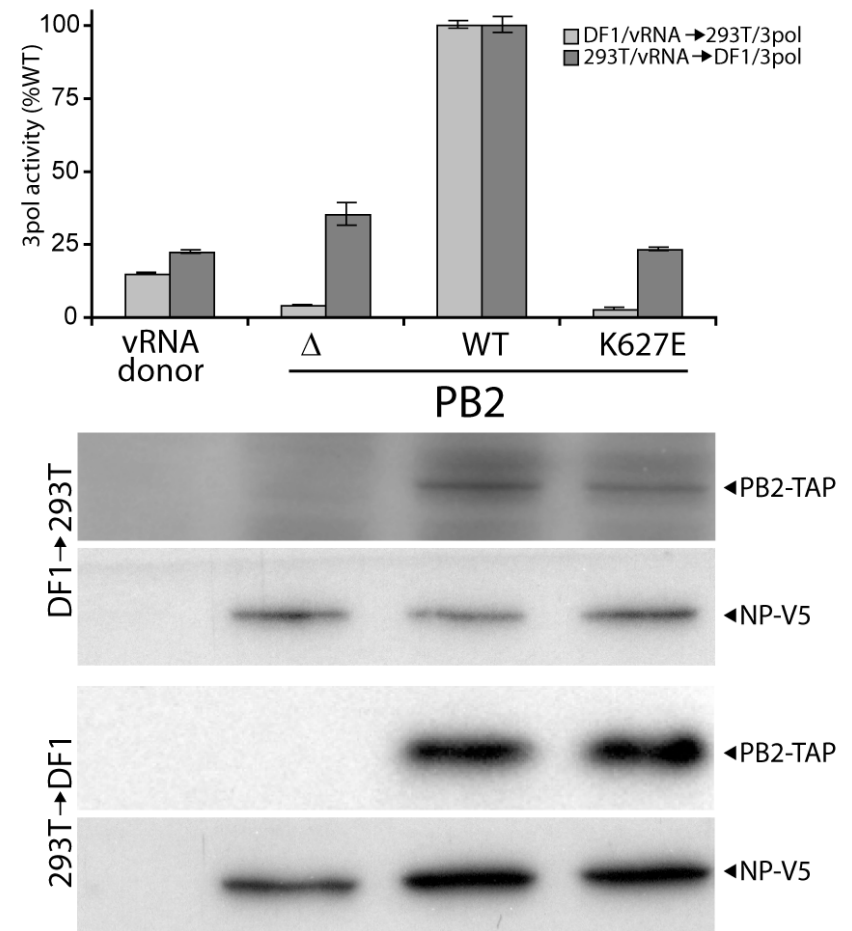
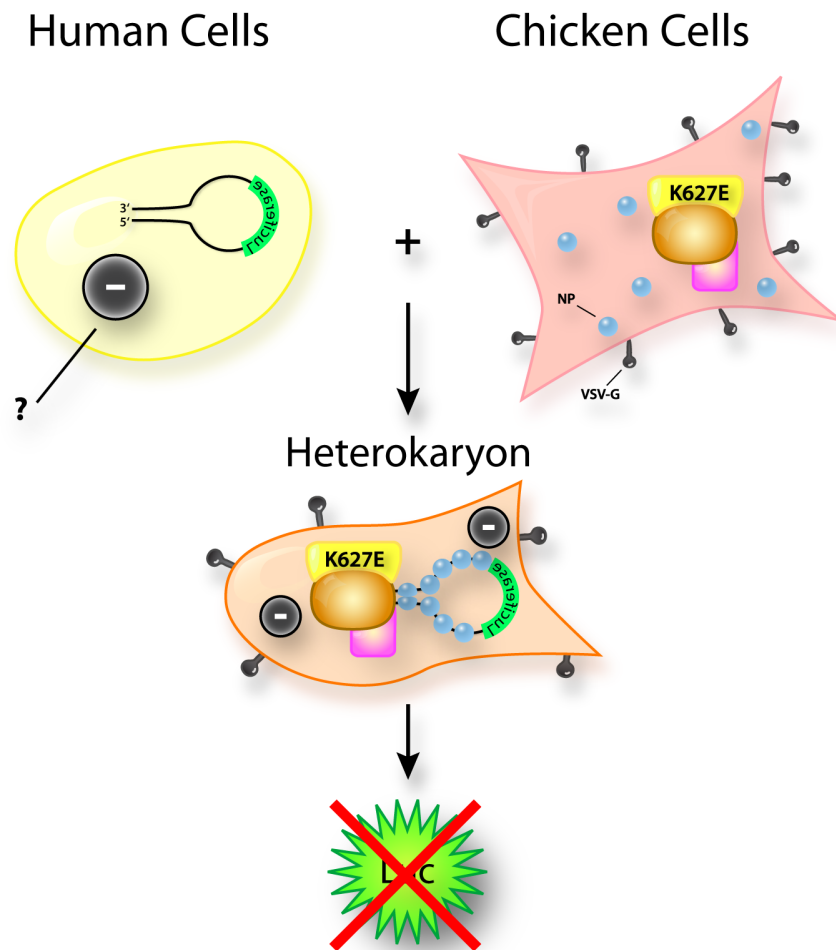
Compensatory Factor?



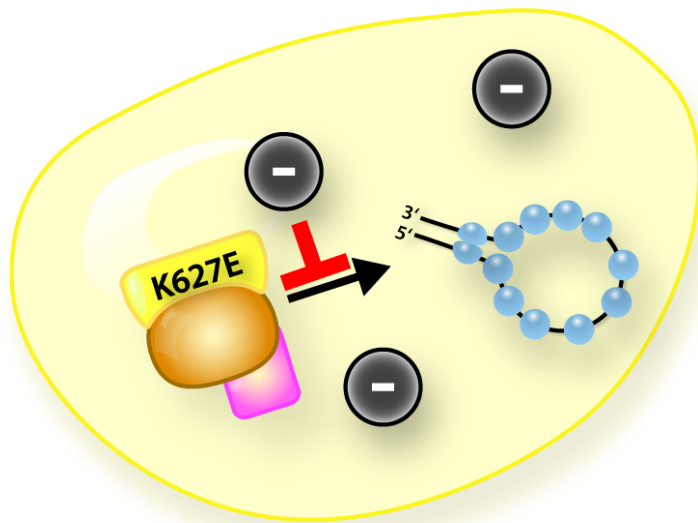
Mehle & Doudna 2008

A dominant inhibitory activity restricts PB2 in human cells

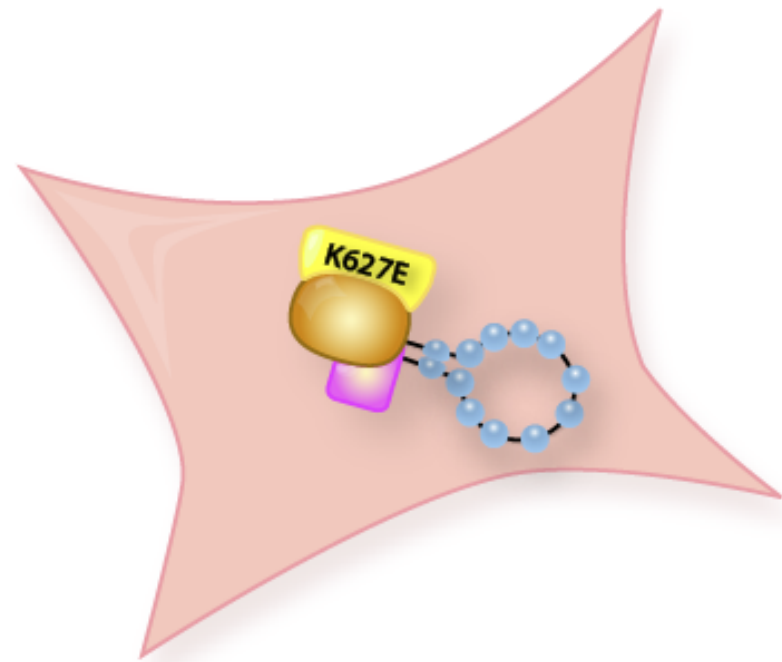
Inhibitory Factor?



A model for restriction of PB2 K627E



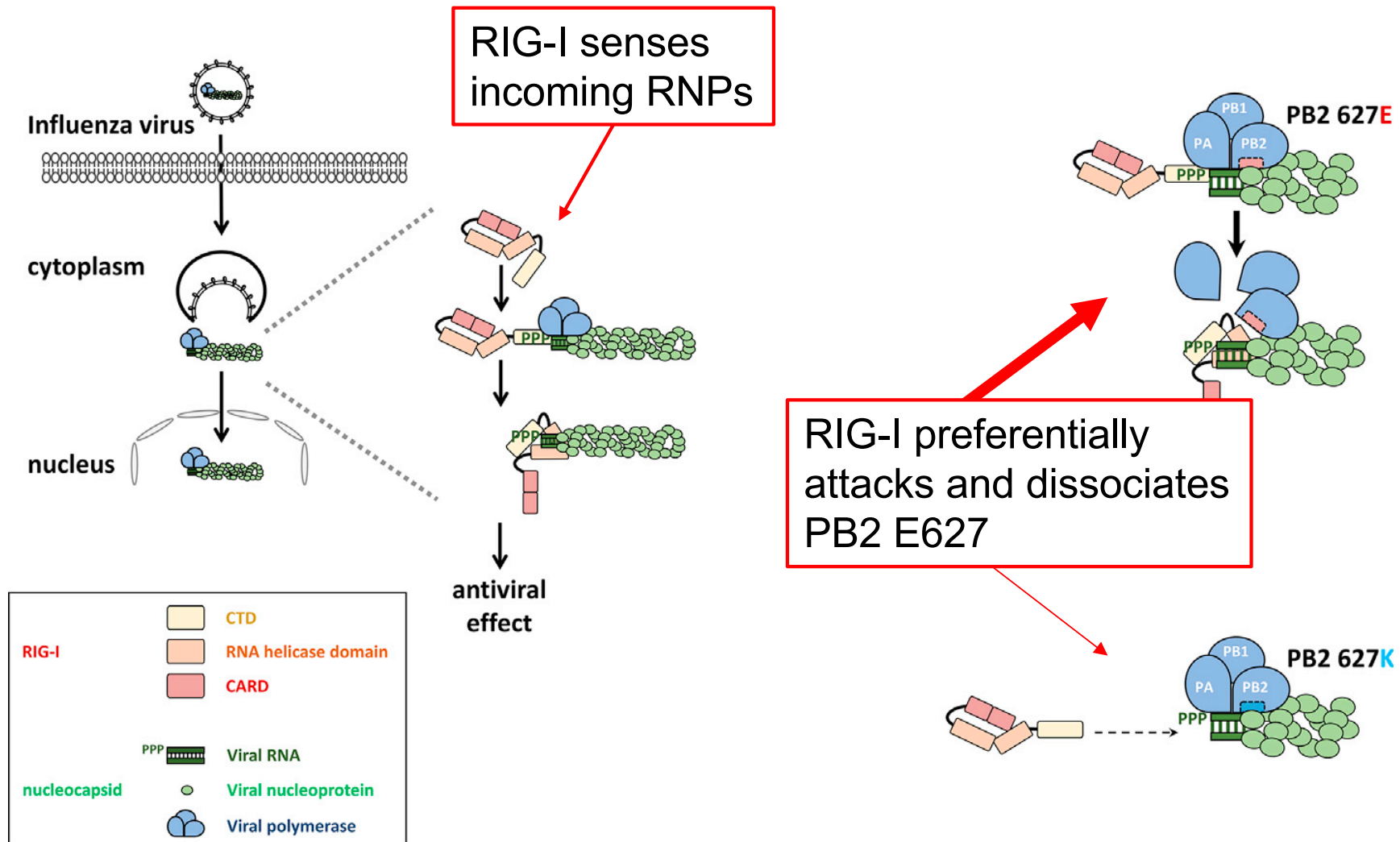
Human Cells



Chicken Cells

Species-specific restriction of PB2 by RIG-I

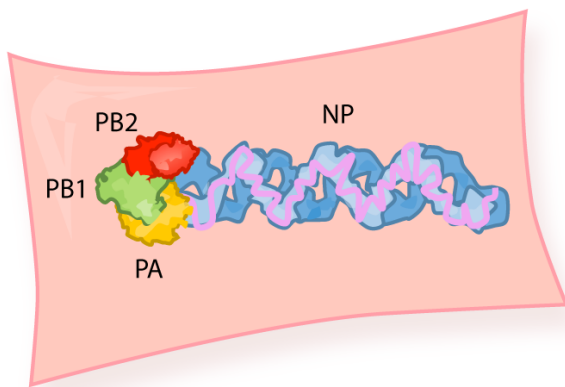
RIG-I – cytosolic sensor, recognizes 5' ppp on RNA, initiates antiviral signaling
– absent from chickens



ANP32A, a species-specific co-factor

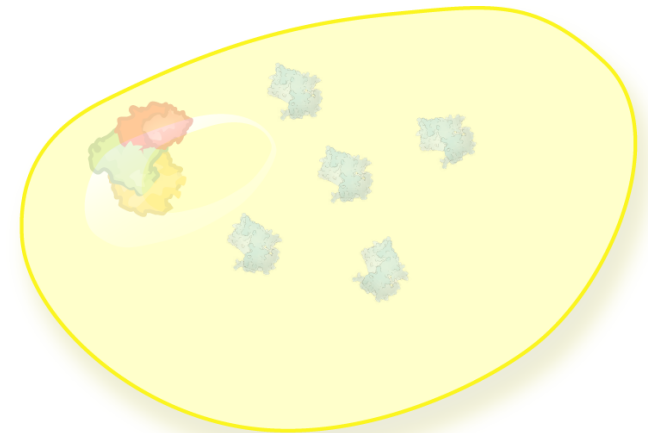
- The Barclay lab reached the opposite conclusion, that PB2 E627 was missing an important co-factor in human cells

Chicken cells



High polymerase activity

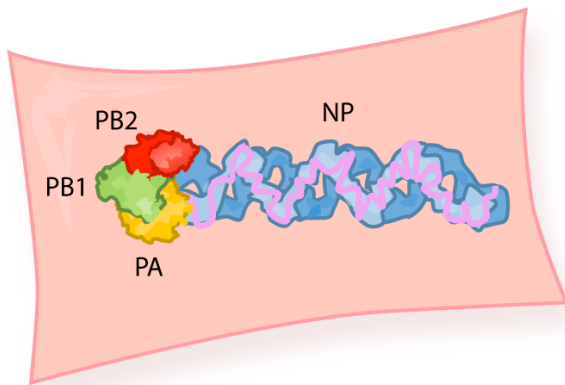
Hamster cells



Restricted polymerase activity

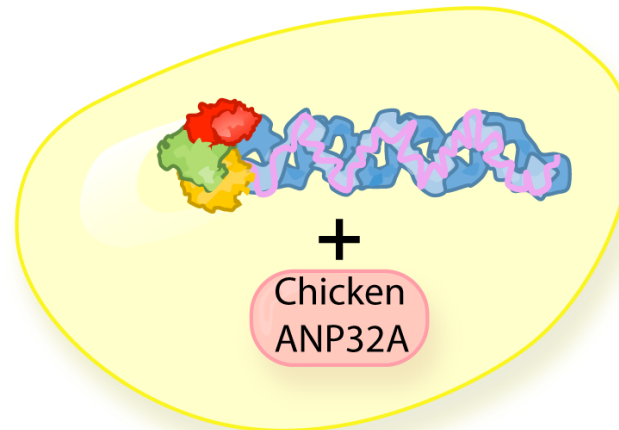
ANP32A, a species-specific co-factor

Chicken cells



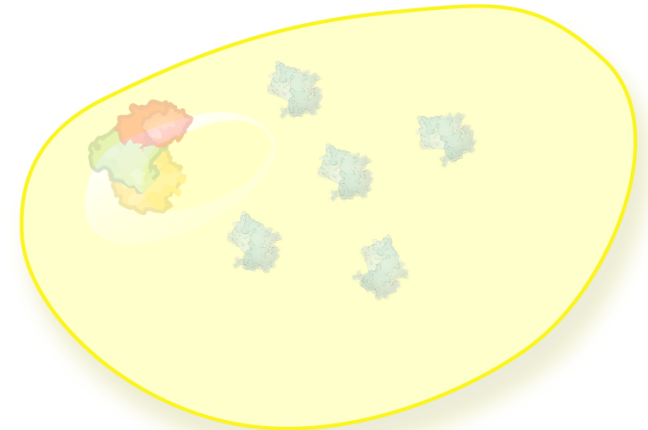
High polymerase activity

Radiation hybrid cells



Rescued polymerase activity

Hamster cells



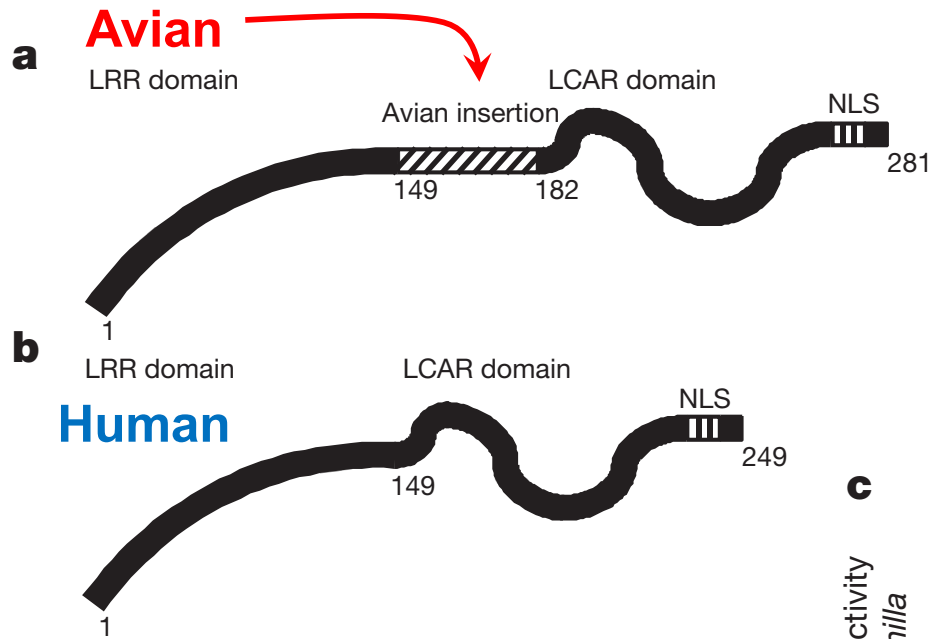
Restricted polymerase activity

ANP32A

- N-terminal leucine-rich repeats, highly acidic low-complexity C-terminus,
- transcriptional control, cell death, mRNA trafficking, and suppressing PP2A

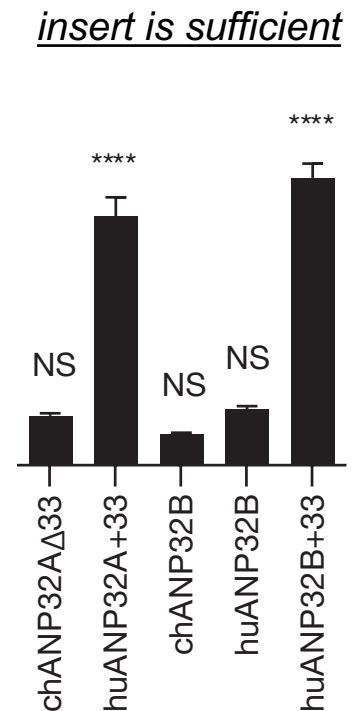
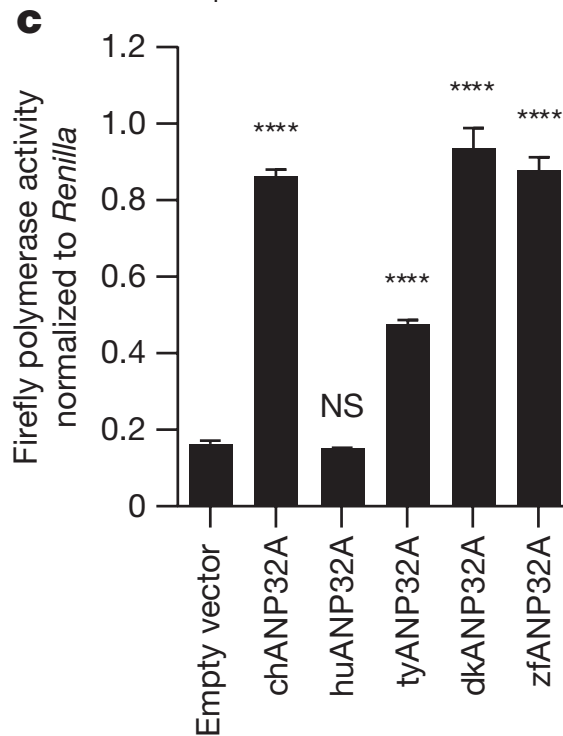
Previously identified, along with ANP32B, as co-factor during vRNA synthesis

ANP32A, a species-specific co-factor

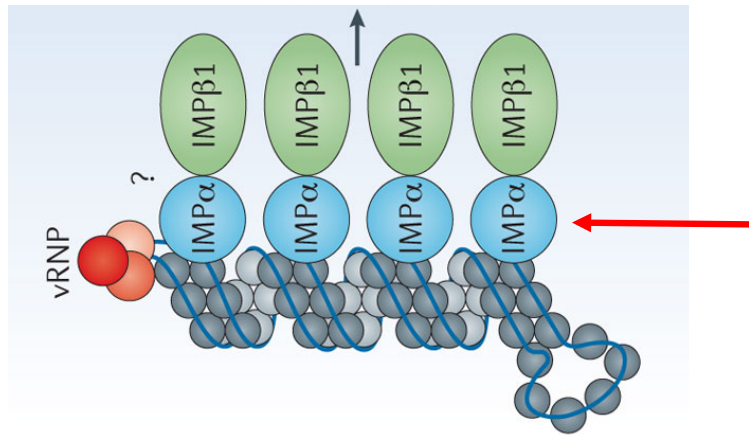


avian insert (exon duplication)
arises multiple times in birds

How does ANP32A rescue function?
Is this related to its other activities?



Nuclear import as a species-specific regulator



IMP α , adaptor for classical nuclear import
6 IMP α 's in human and birds

Avian PB2 prefers IMP α 3, human PB2 prefers IMP α 7

PB2 D701N can occur during adaption of avian PB2 to mammals
partially overcome restriction of an avian polymerase

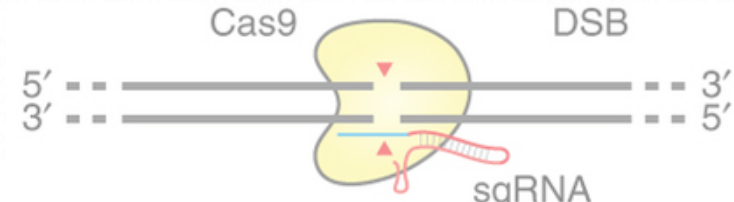
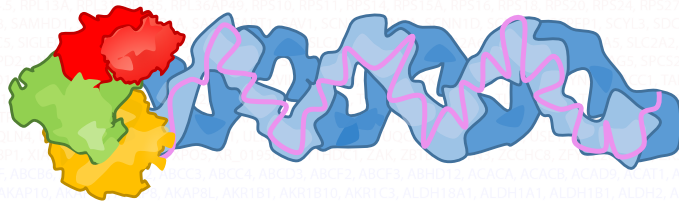
Using a heterologous NLS (i.e. SV40) cannot overcome this defect, suggesting
a post-entry function for IMP α 's, possibly chaperoning PB2 into trimer

Does IMP use control host range? Especially in presence of PB2 K627?

RNAi:AATK, ABCB10, ABCC10, ABCC6, ABCD1, ACACA, ACE2, ACOX1, ACP2, ACR, ACSL1, ACSL4, ACTC1, ACTL6B, ACTN2, ACVR1C, ACVR2A, ADAM8, ADAMTS1, ADAMTS2, ADAMTSL4, ADAT1, ADCY7, ADRA18, ADRB2, ADRBK2, AFF2, AGTRAP, AHCY, AHCYL1, AHNAK2, AHR, AIG1, AKAP11, AKAP13, AKT1, AKT3, ALA51, ALG10, ALG6, ALPK2, AMHR2, AMMECR1, AMN, AMOTL1, AMOTL2, ANAPC2, ANGPTL3, ANKK1, ANKMY2, ANKRD2, ANKSE, ANPEP, AP2B1, AP2M1, APB3A, APBB1A, APC, APC2, APOA1, APOA5, APOBEC3G, APOLE, AP, APPBP1, APO4, AQR, ARAF, ARCN1, ARD1, ARLA4, ARMC6S, ARNT, ARNT, ASAH1, ASHA, ASCA, ATCHAF, ATF1, ATF2, ATF4, ATG16L1, ATG13A1, ATPIA2, ATP1A3, ATP2C1, ATP5B, ATP5C1, ATP5F1, ATP5L, ATP6A1, ATP6A2, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V0E2, ATP6V1A, ATP6V1B, ATP6V1B2, ATP6V1I1, ATP8, AXIN1, X2N, B3GALT2, BACE1, BACH2, BAIDP, BAIPA1, BAIPA3, BARN BARHL2, BCAS2, BCL10, BCL1, BCL2, BCL6, BCL2L1, BID, BIRC1, BIRC8, BLNK, BMPR1A, BMPR1B, BMPR2, BRPF1, BRWD3, BST2, BTG1, BUB1B, BUB3, BZRAP1, C10orf57, C11orf60, C11orf82, C12orf47, C12orf5, 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Goal:
Identify novel human host factors that regulate the influenza virus replication machinery

Post-translation control of the RNP Exploiting antiviral responses



Arindam
Mondal



Tony Dawson



Vy
Tran

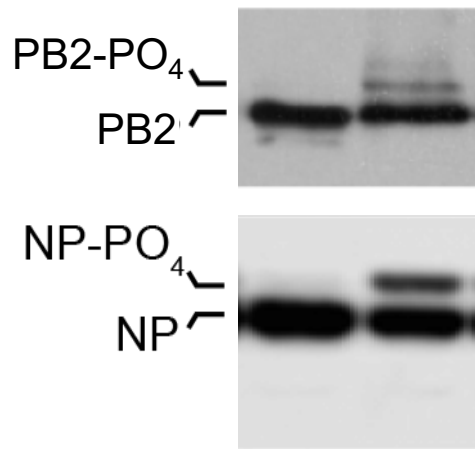


Mitch
Ledwith

ATP6V1B2, ATP6VOD1, AXL, B3GAT1, BAD, BPTF, BRCA1, BTC, BUB1, C11ORF81, C13ORF28, C17ORF85, C1ORF56, C1QL3, C4BP4, C4ORD35, C6ORF136, C6ORF162, C6ORF57, CAMK1, CCN1L, CD200R1L, CDH26, CDKN1A, CEBPG, CENPH, CENPK, CFL1, CHMP2A, CLEC110A, CLOCK, CMTM1, COX5B, COX7B2, CBRN, DAPK2, DCLE1C, DDXK3, DLAT, DOK3, DPPA2, DR1, DSG4, DYRK1A1E, EED, EGRF, EIF2B1, EOMES, ERCC4, FBXO15, FBXO8, FMO2, FSHB, GAPDH, GAS2, GC, GIGYF2, GC1, GON4L, GPR151, GULP1, HACE1, HCG_1986447, HIF1T1H1B, HIF1T1H2AB, HPS4, HRAS, HPS2, HR77, IFIT2, ILF1D1, ILF2, ILF3, ILF4, ILF12, INPP4A, IPP, ITIH, ITGAM, ITGAX, IVN1SAB16KCN, KIAA0174, KIAA1751, KIF24, LARP6, LHX8, LCG339766, LCG730139, LRRCS9, LPM1, MADD, MAEA, MALTI1, MAML3, MAN2B2, MAPK10, MAPK13, MAPK9, MDM2, MED6, MERTK, METAP1, MLLT11, MPG, MSH6, MHR1, MS2, NCRNA001020, IGF2BP3, NEK3, NMBR, NRGI, NUP214, NUP85, NUP1L, NXC3, ORZV1, OR5A21, OR5M21, P2RY12, PAB5A, PCDH12, PCDH9A, PDGFRA, PKC3A, PLAT4, PLEKH11, PLK4, POLB2, POLE2, POLR2J2, PQLC1, PSM2D1A, PTFAR, PTFD51, PTGER2, PTPN13, PTPRJ, PYL, RAB7A, RABGA1P, RAD23A, RARS2, RBPJ, RCVRN, RNKSF3, RPK3, RPL1, RNF19A, RNF24, RPL23, RP525, RP525, RPS1B, SAGE1, SCG2, SELPLG, SENP1, SERPINA1, SH3BP4, SIN3B, SIPA1, SLC20A1, SLC7A1A, SLC7A4, SMARCE1, SMOG1, SMPD2, PNTB2, SP100, SPOCK2, STSLC1A, STARD5, STX5, TFAD8, TASF2B1R, TCD12B, TCF2, TFP12, TFI12, THOC6, TMC6, TME4M11, TMEM141A, TMTCT4, TNOF12 TNSF5F13, TNSF5F13, TNSF5F9, TNRC6A, TRP22, TRIM13, TRIM16, TRIM16L, TRIM21, TRIM5, TRM1, TXNDC16, UBXN7, UGT2B15, UPLF4, USP22, USP34, USP37, USP44, USP8, WNK2, WY1, XCR1, YPEL2, YWAH, YWY, ZCCHC1A, ZCCHC4, ZNF251, ZNF397, ZNF71, ZSCAN12, ZSCAN16 **random, homozygous insertion:ADAM20, AKT1, ARID1B, CHM, COG5, COX5A, CSNK1D, DDX17, DDX58, GRK6, HEATR7A, HTRC6, LMR16, L5A, MDN1, MRSP4, N4BP2, NDUFA7, NDUFAF2, PKD2L2, RAD51L1, RHGF, SF3A1, SLC5A25, SLC30A9, STXB1, VP53, ZFP2 haploid screen:CMAS,SLC35A2**

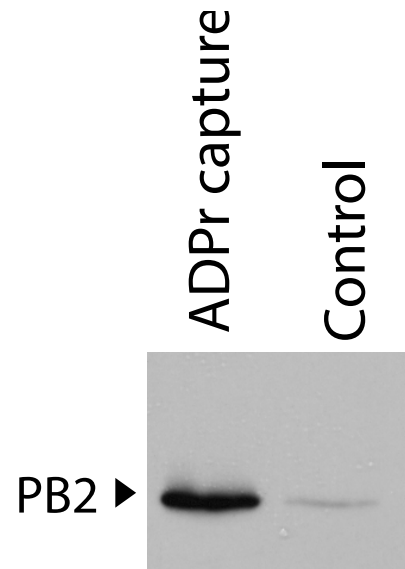
Post-translation regulation of the viral replication machinery

Phosphorylation



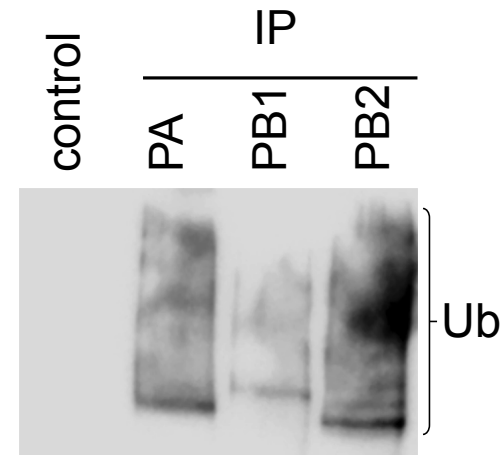
Mondal, 2015
Hutchinson 2012
Kistner 1985, 1989
Privalsky 1977

ADP-ribosylation



Liu 2015
Mehle unpub.

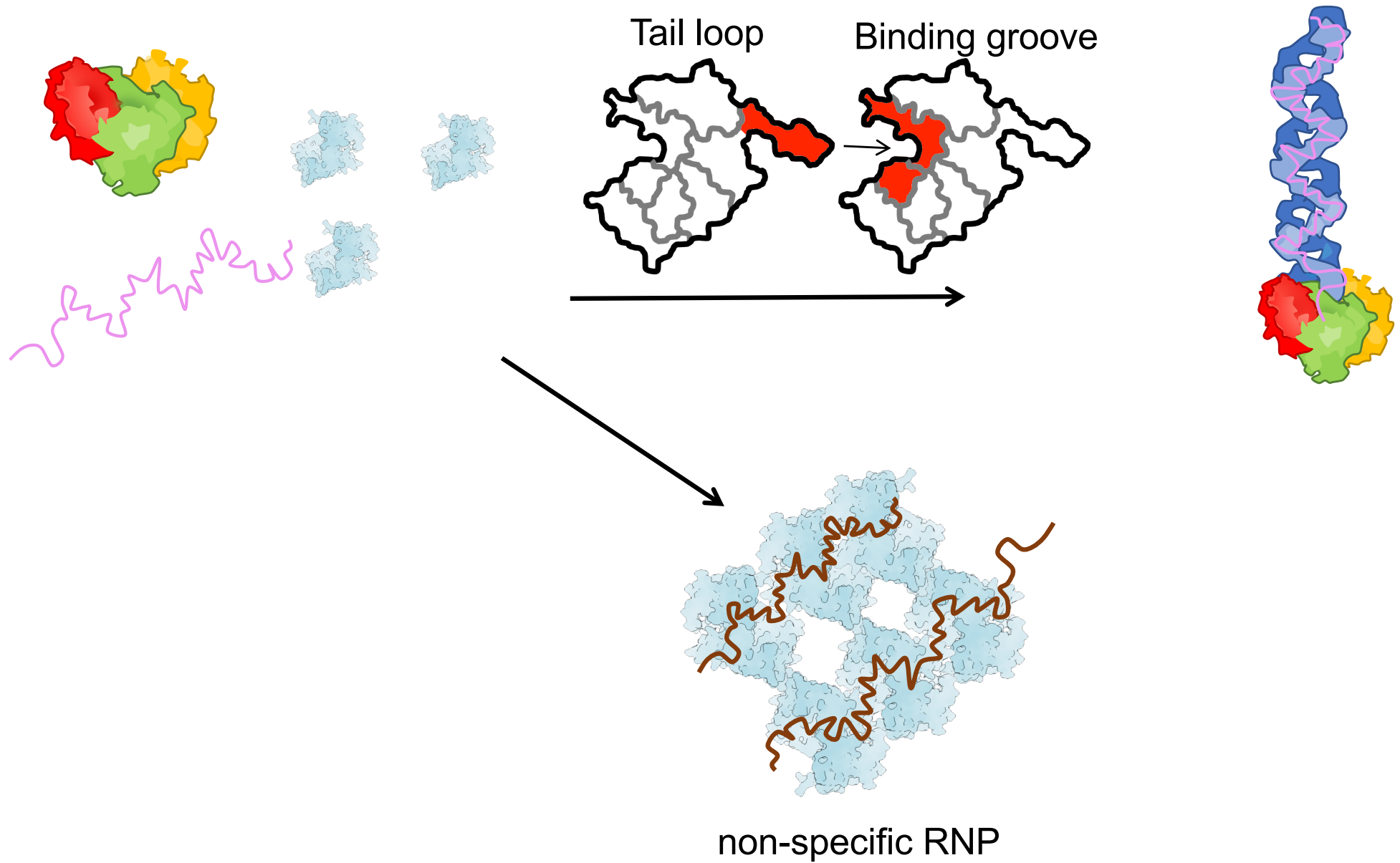
Ubiquitination



Kirui 2016
Liu 2015
Lin 2017
Liao 2010

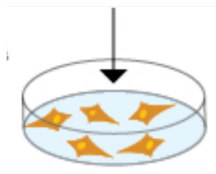
Others?

The influenza RNP

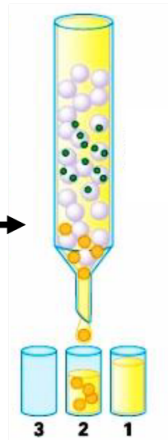


Phosphorylation of NP maintains a monomeric state

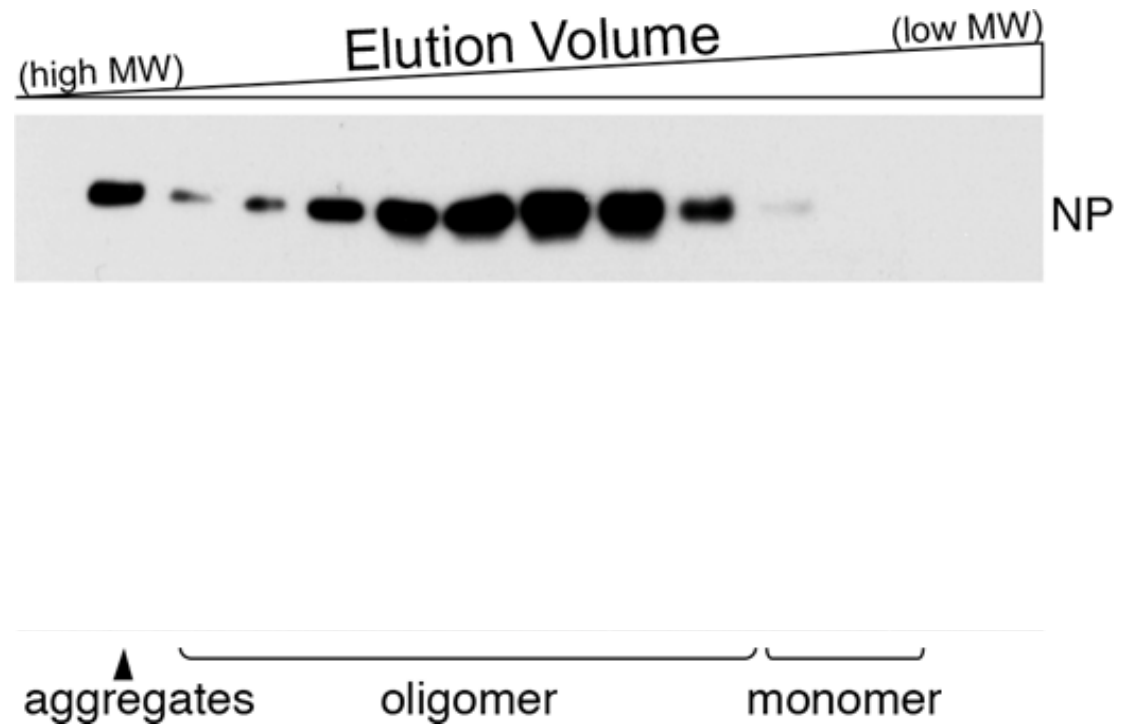
NP expression in
293T cells



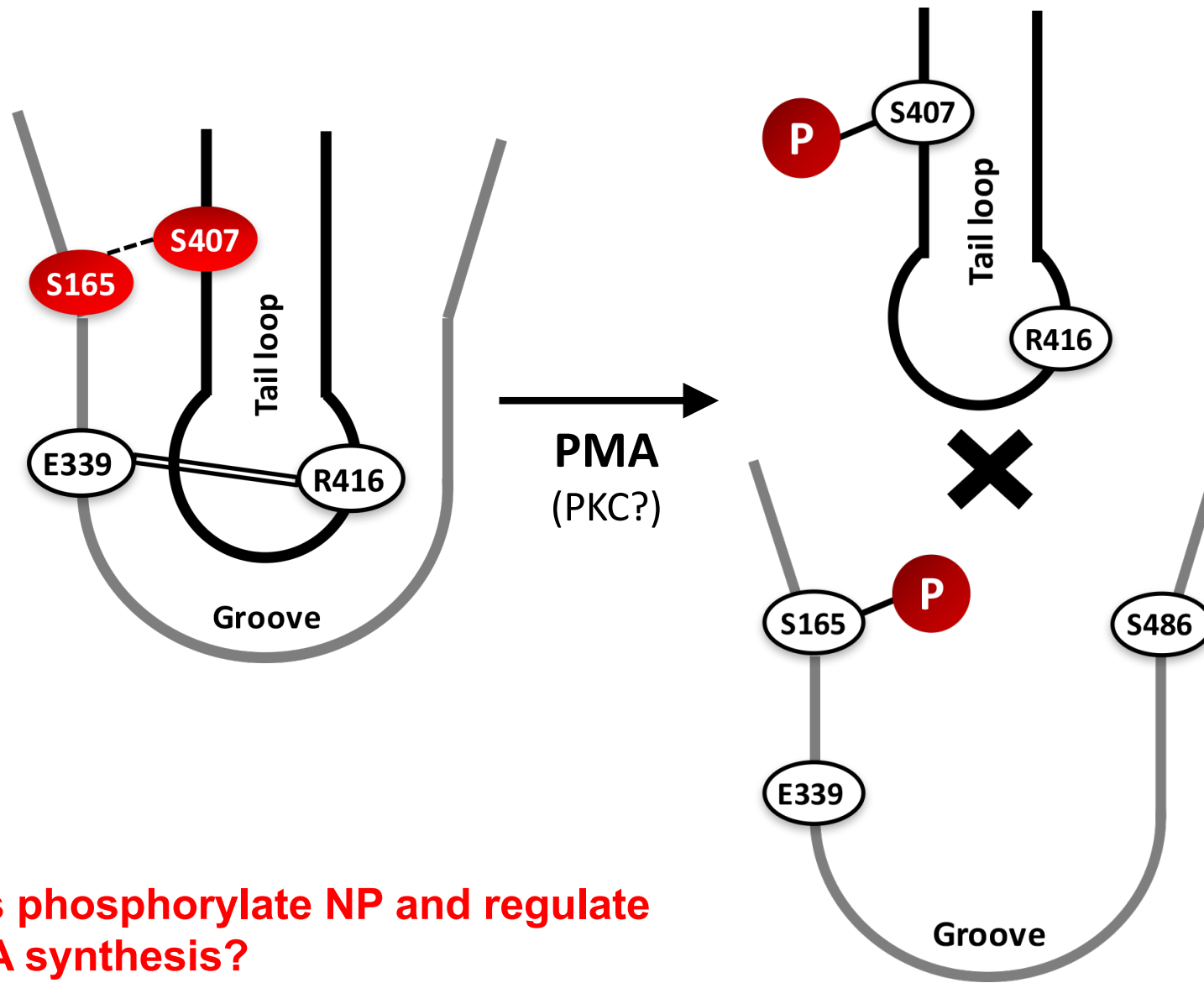
Lysis



Gel-filtration
blot for NP



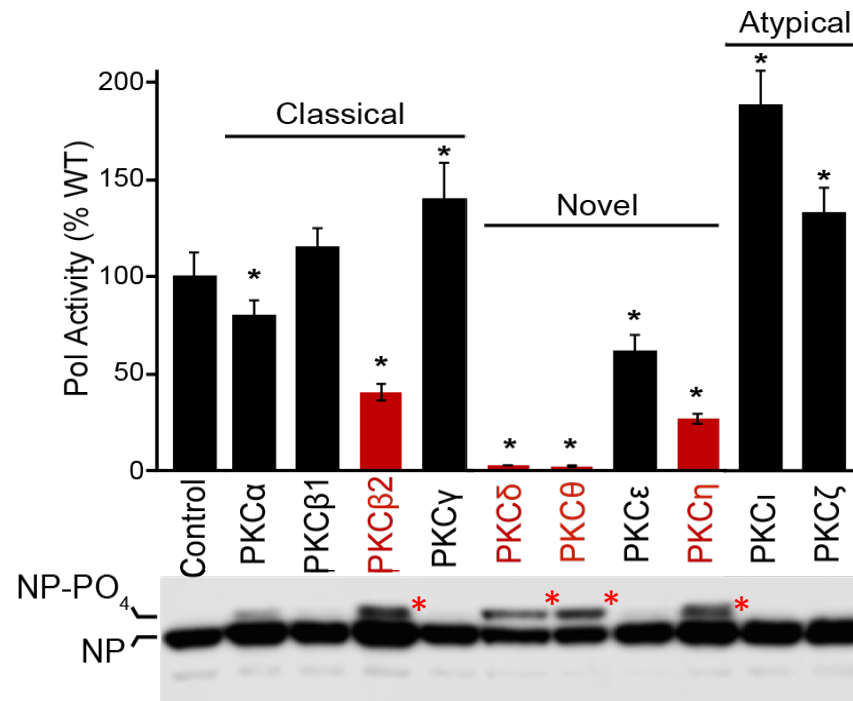
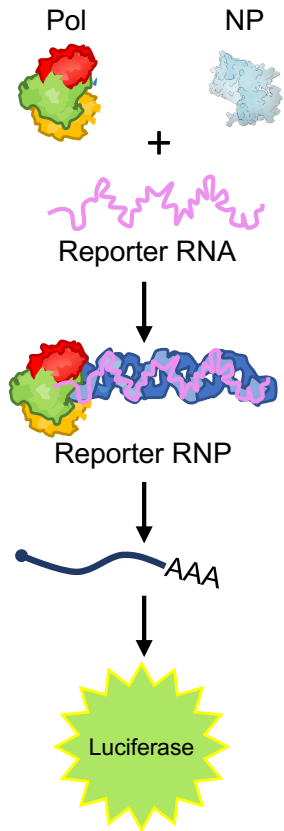
Phosphorylation of NP maintains a monomeric state



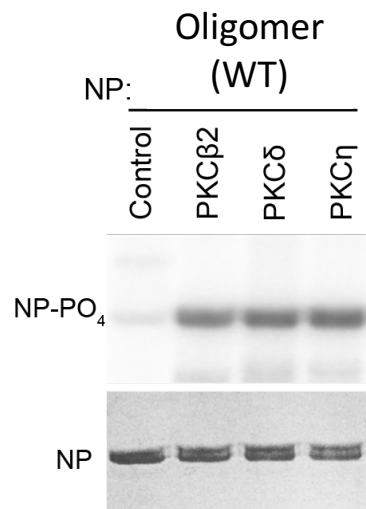
Do PKCs phosphorylate NP and regulate viral RNA synthesis?

Constitutively active PKC isoforms alter polymerase activity

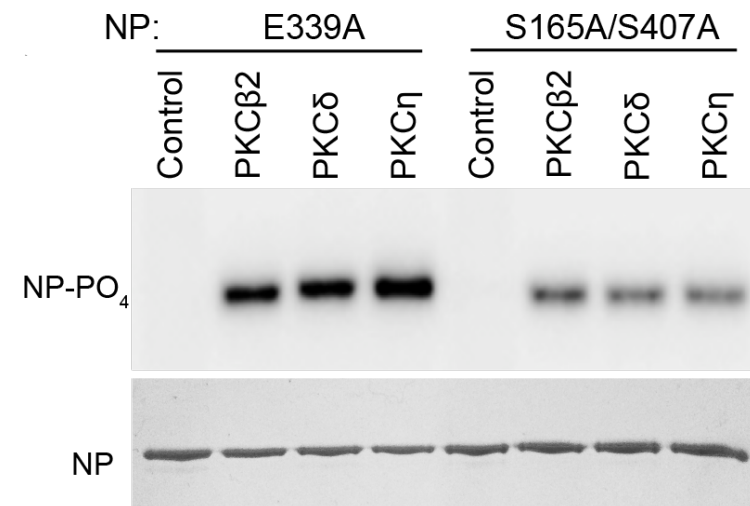
Pol Activity Assay



PKC phosphorylates NP S165 and S407 *in vitro*



Phospho-sites occluded
in NP oligomer

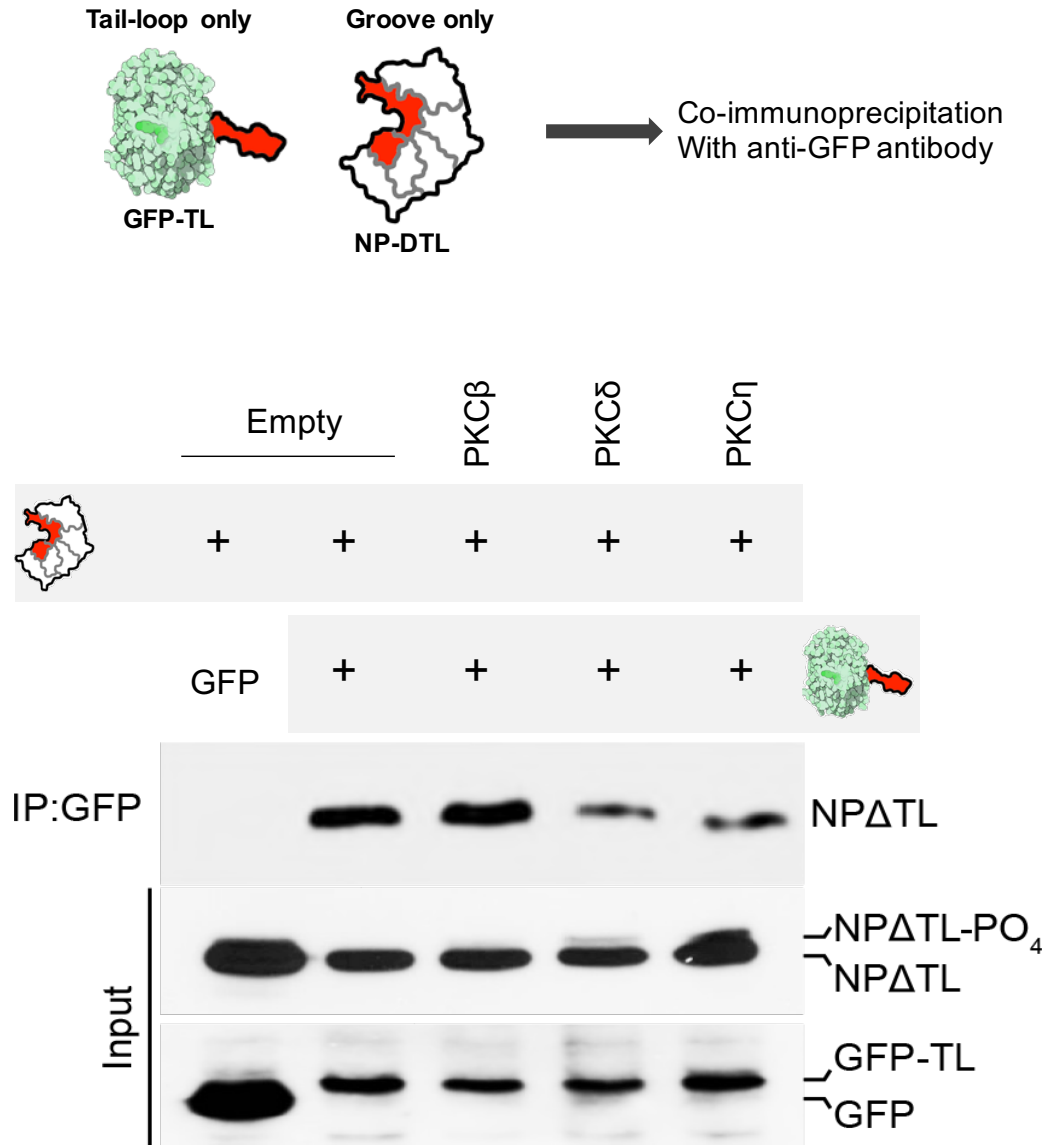
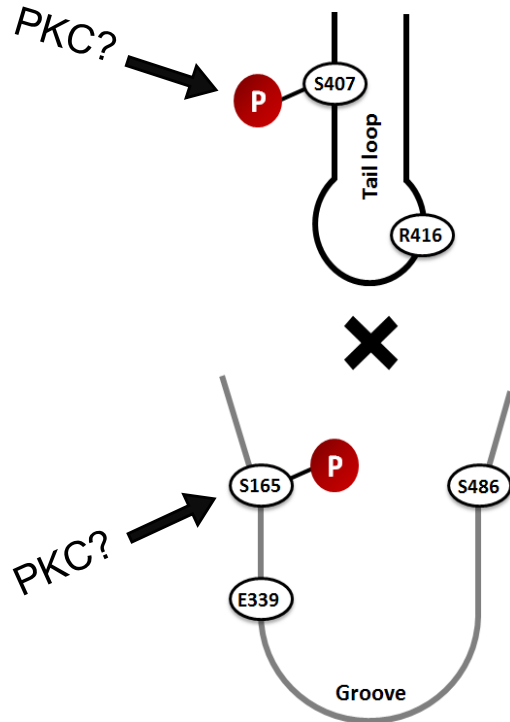


NP S165 and S407 are
PKC targets

In vitro kinase assays with purified PKC and NP

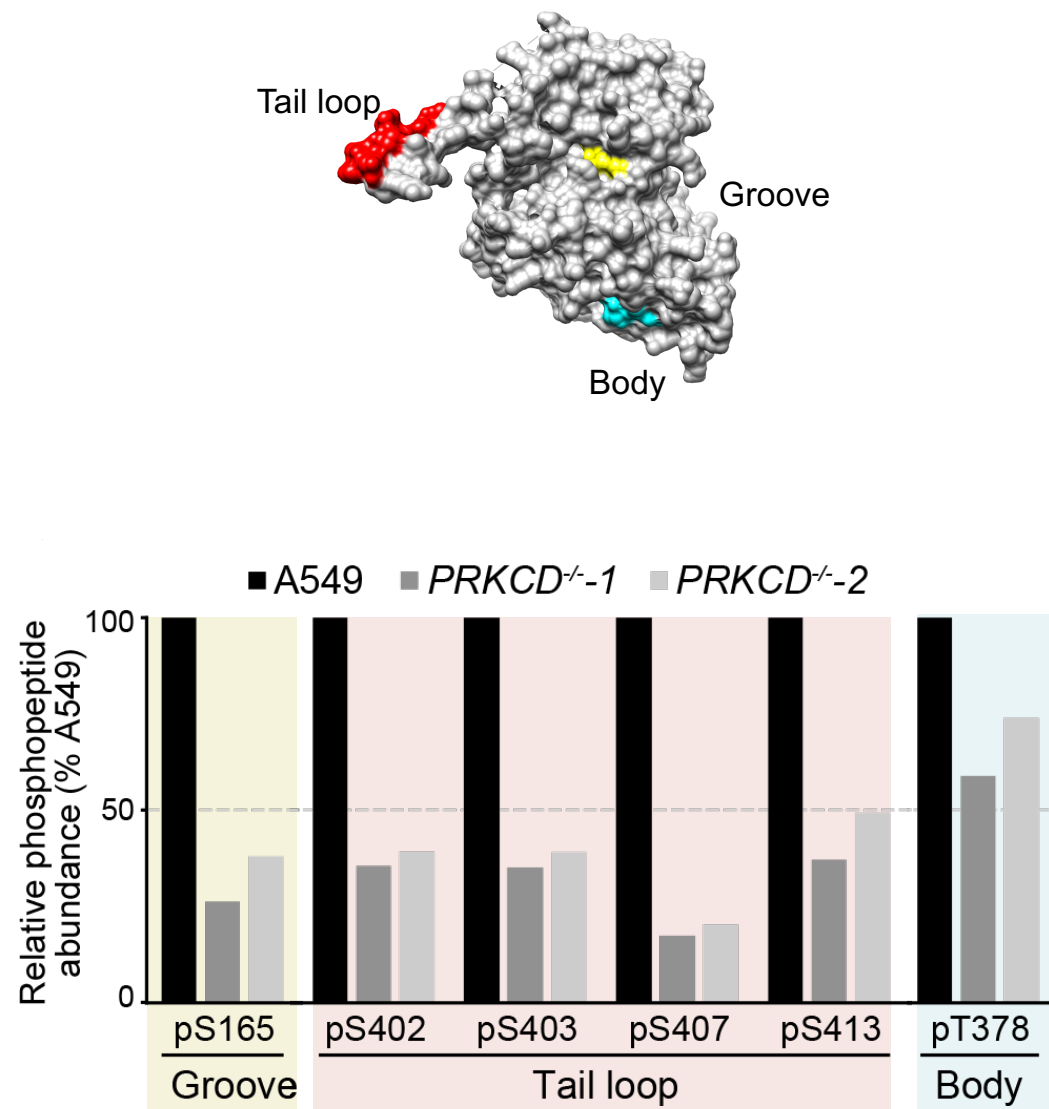
Phosphorylation of S165 and S407 by PKC inhibits tail-loop:groove interactions

Tail loop:groove interaction assay



Knockout of PKC δ reduces NP phosphorylation and replication

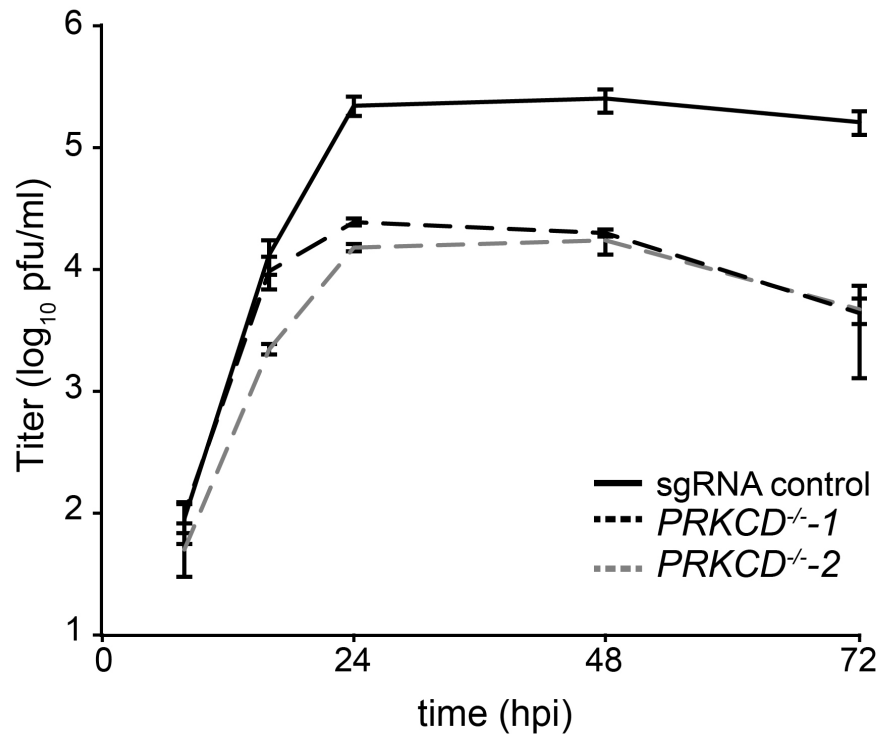
Quantitative mass spectrometry analysis



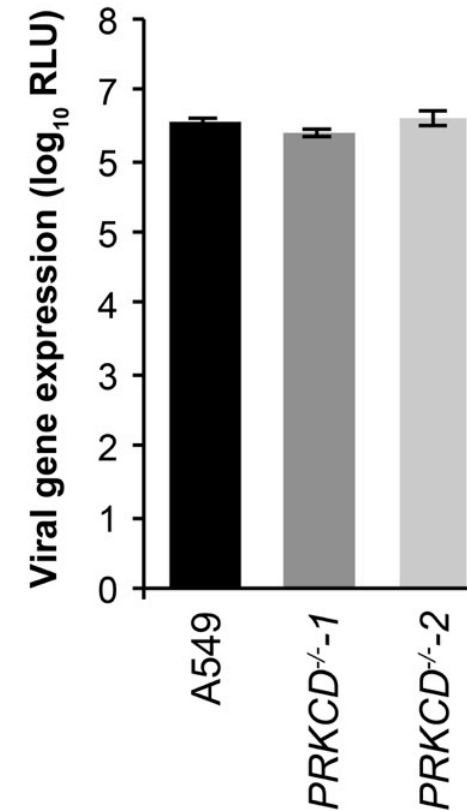
Knockout of PKC δ reduces NP phosphorylation and replication

Viral replication

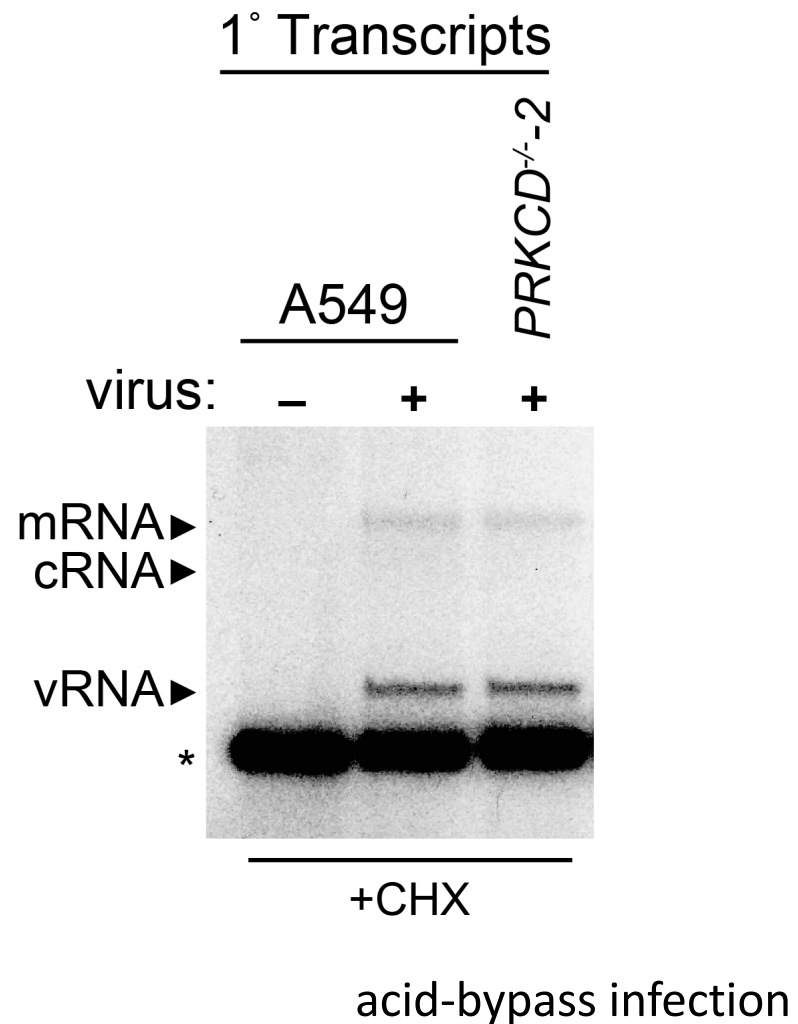
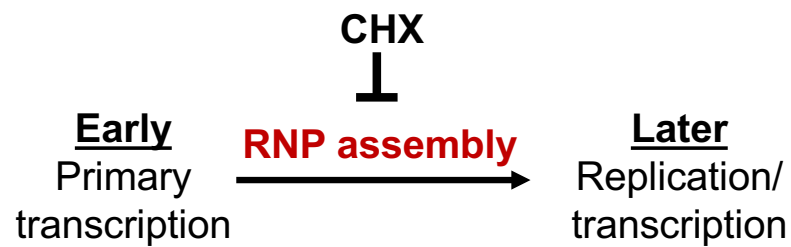
Influenza



West Nile

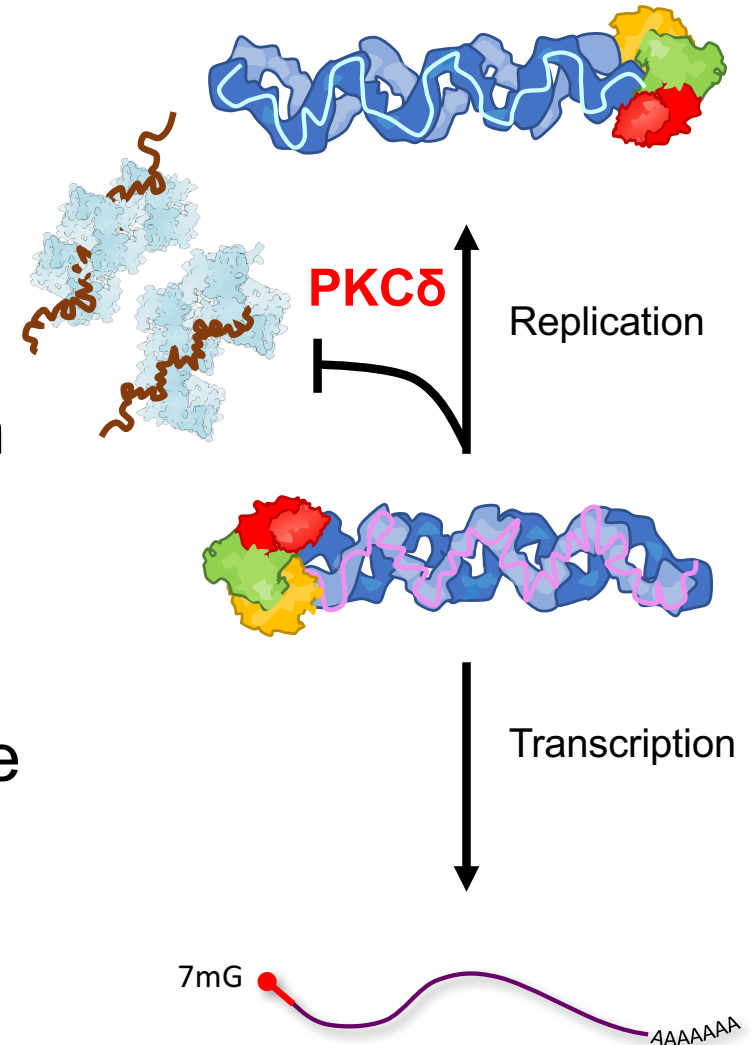


Genome replication is specifically inhibited in PRKCD^{-/-} cells



PKC δ creates a pool of RNP-competent NP

- PKC δ phosphorylates NP S165 and S407, preventing NP:NP interactions
- RNP assembly is severely compromised by *both* over-expression and knockout of PKC δ
- Balanced PKC δ activity controls RNP assembly and the transition to genome replication



What licenses RNP assembly?

Phosphatase?

How is NP recruited and where is it incorporated?

