# Host regulators of the influenza virus replication machinery


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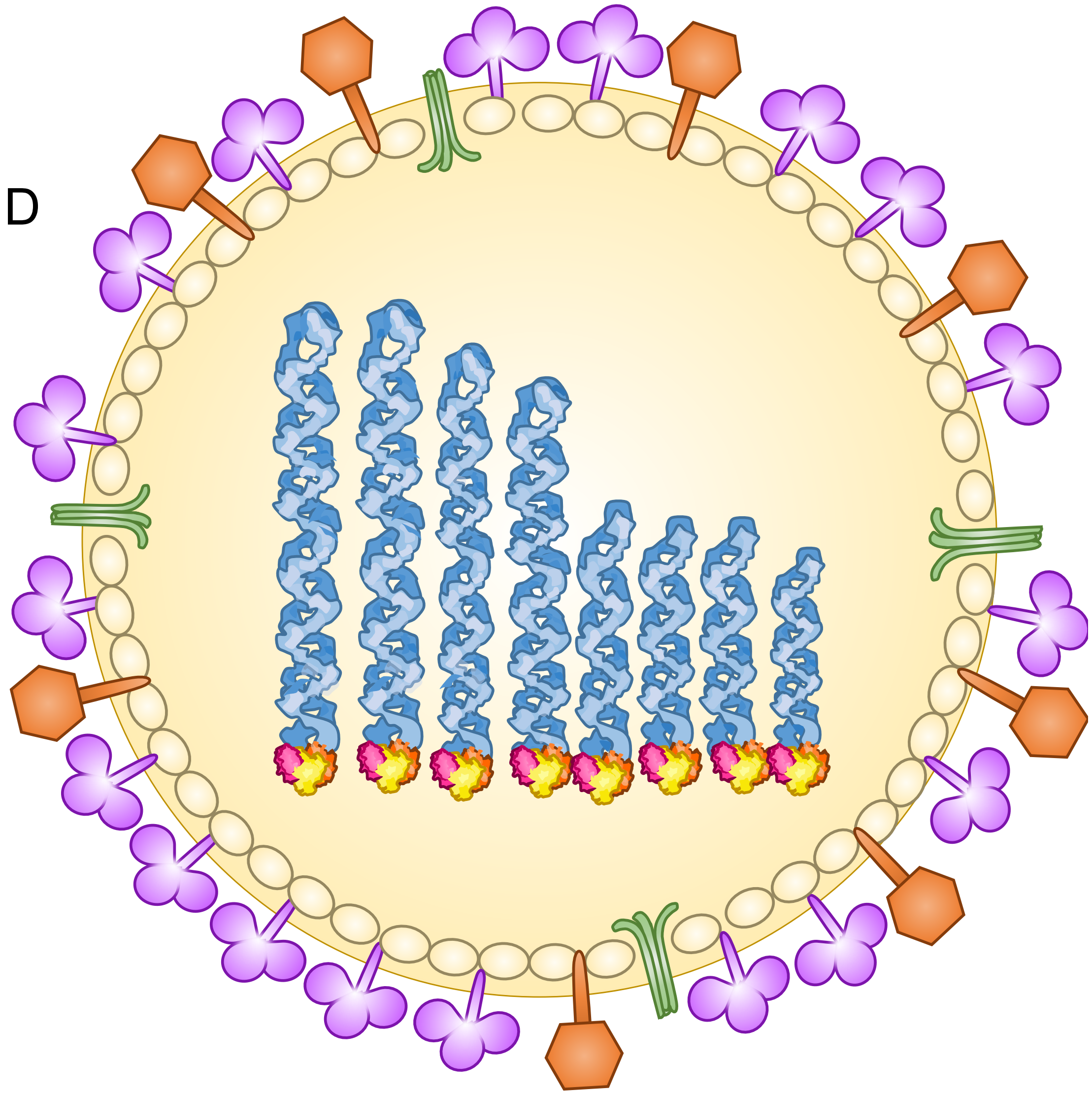
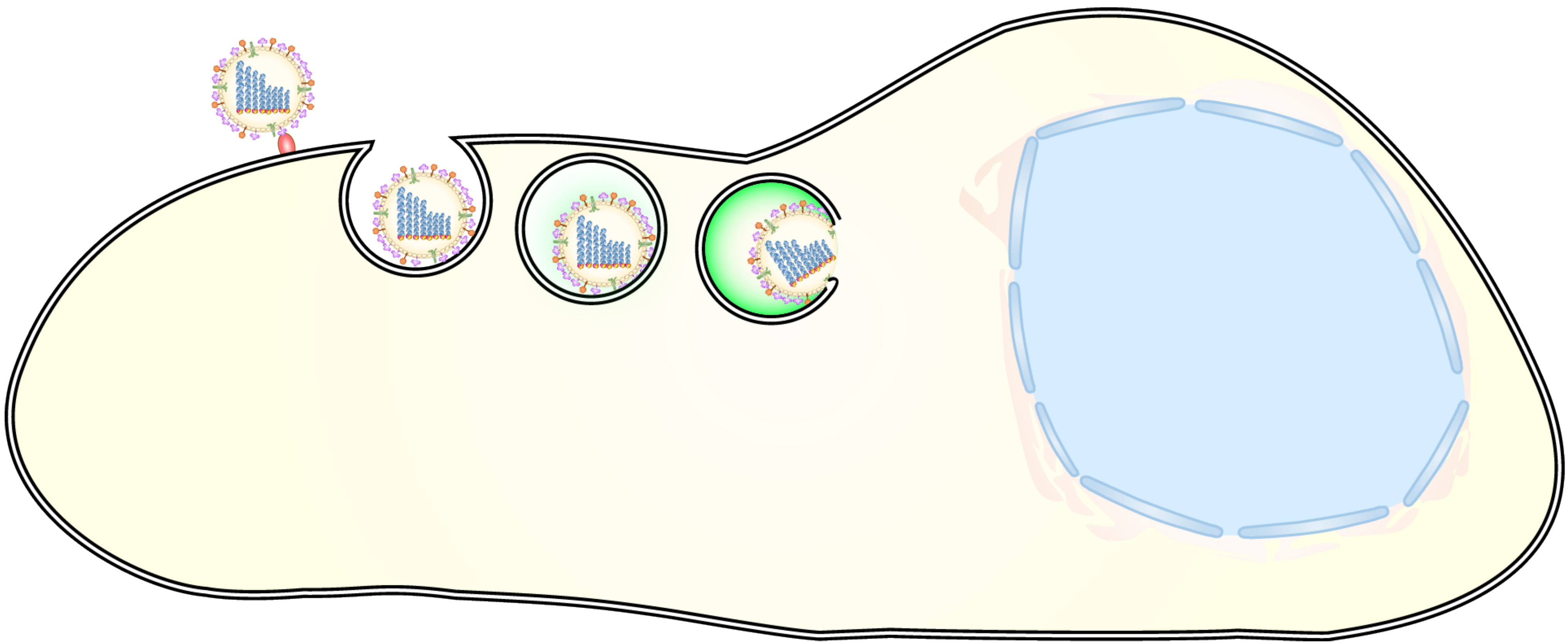
# Influenza viruses

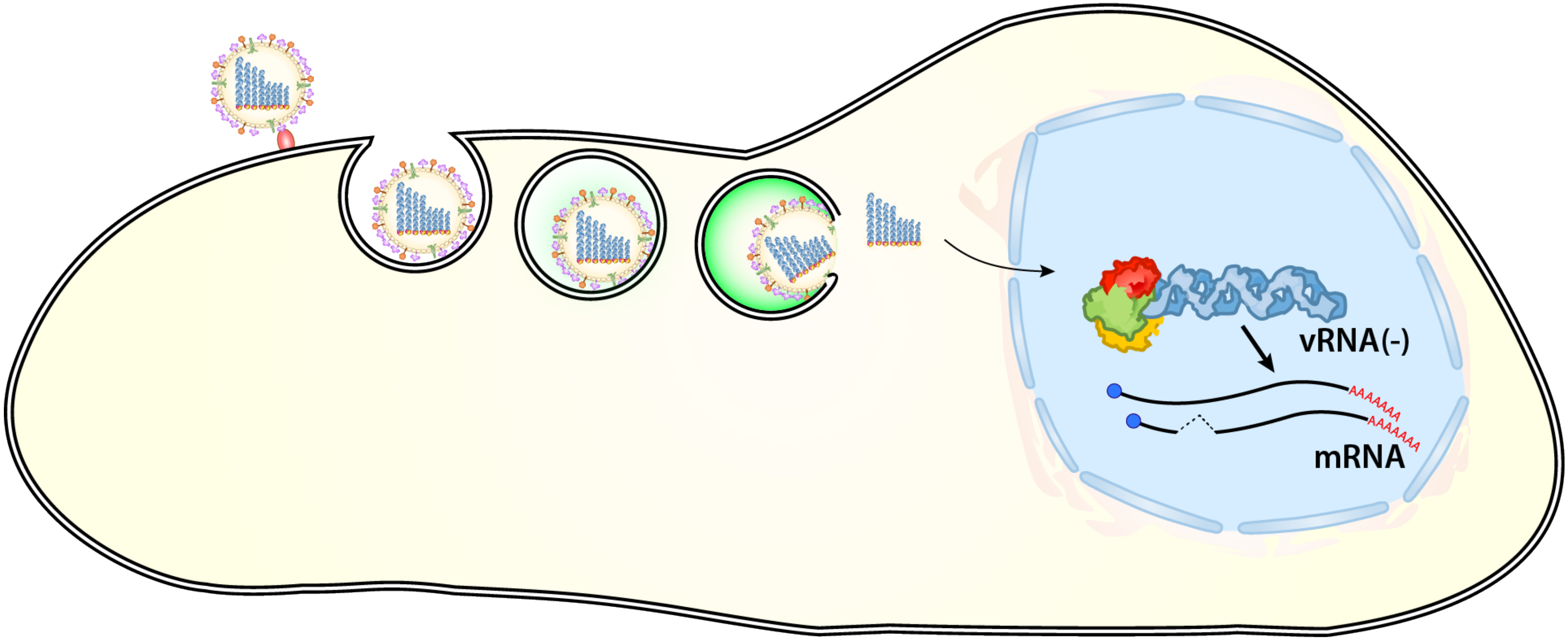
- *Orthomyxoviridae:* Influenzas A, B, C, D
- Surface HA and NA define influenza subtypes (18 HA, 11 NA)
- Negative-sense ssRNA genome
  - 8 segments, ≥ 14 proteins
  - Packaged into ribonucleoprotein complexes (RNPs)



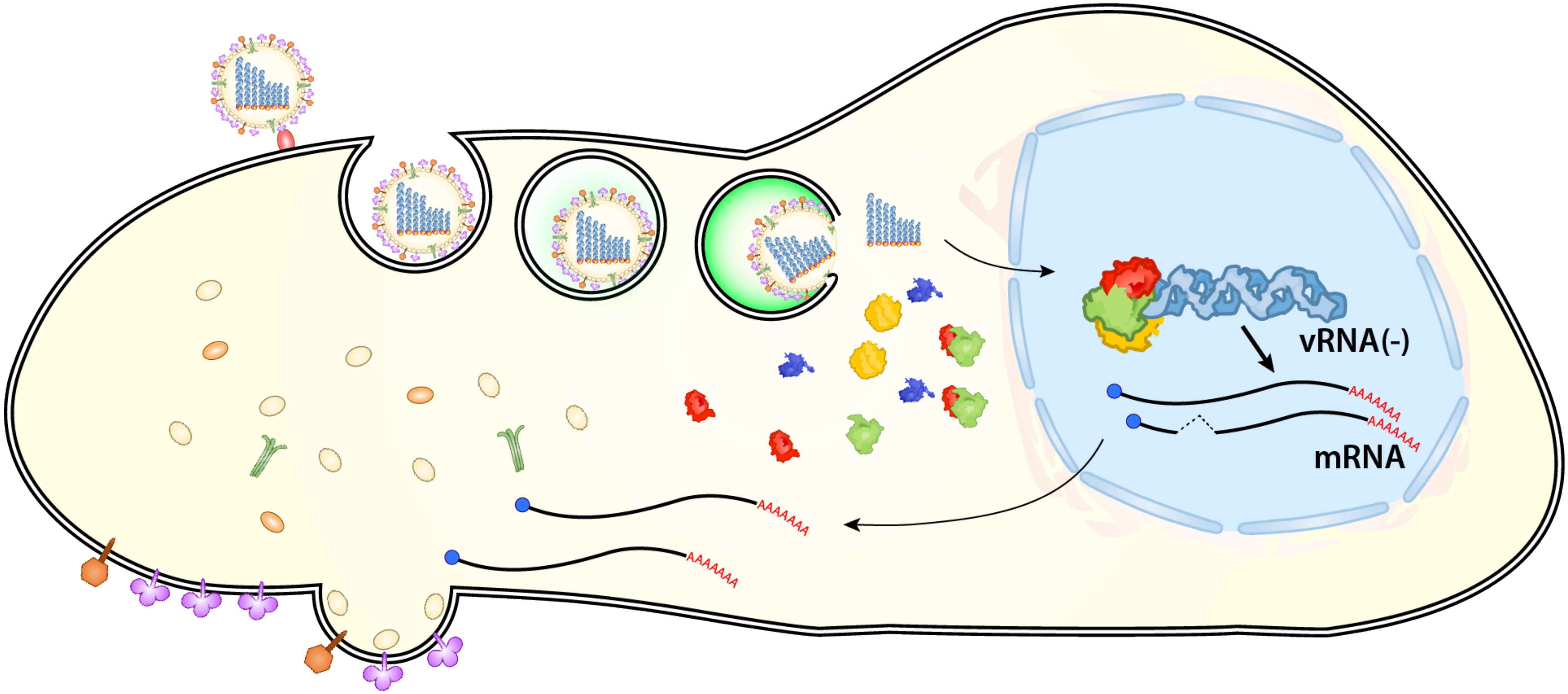
# The influenza virus replication cycle



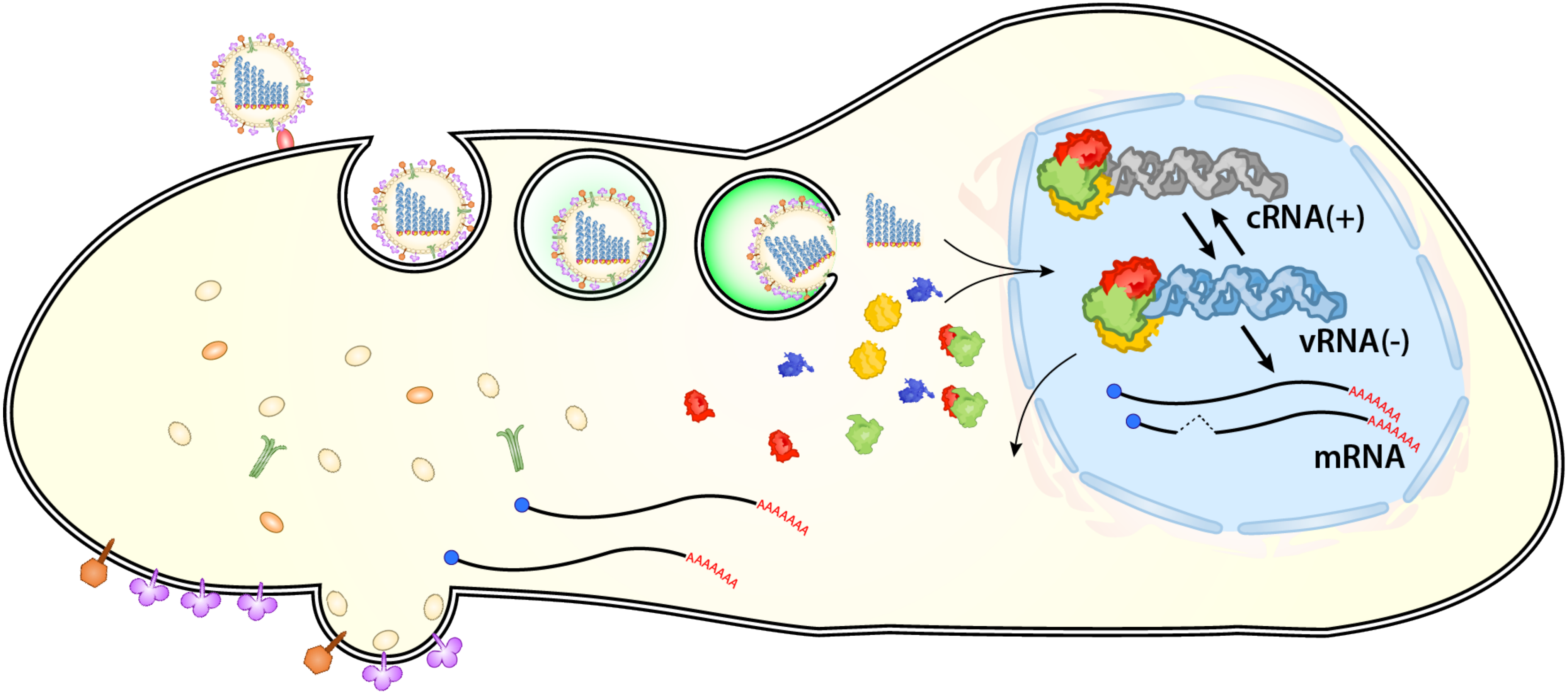
# The influenza virus replication cycle



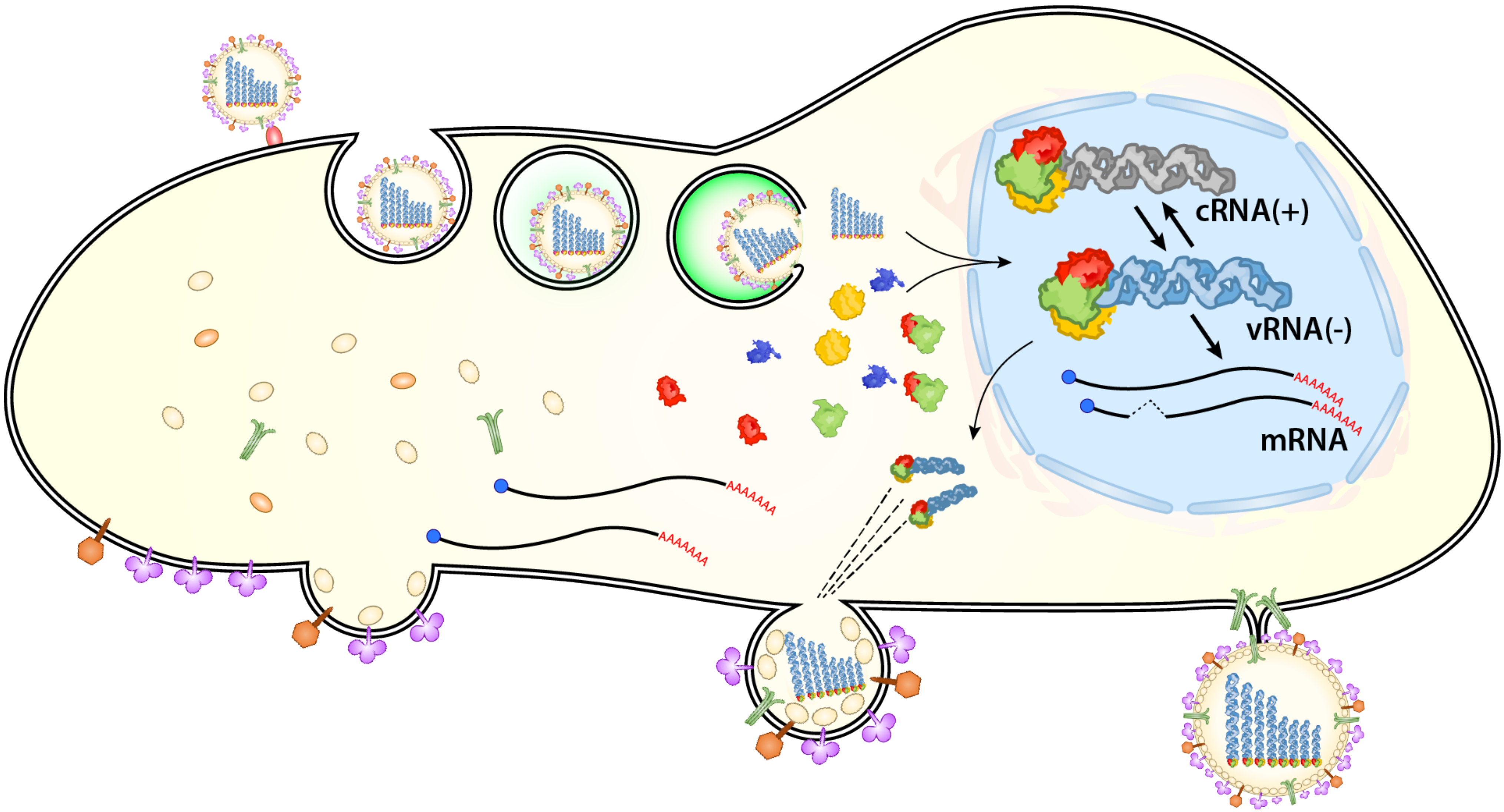
# The influenza virus replication cycle



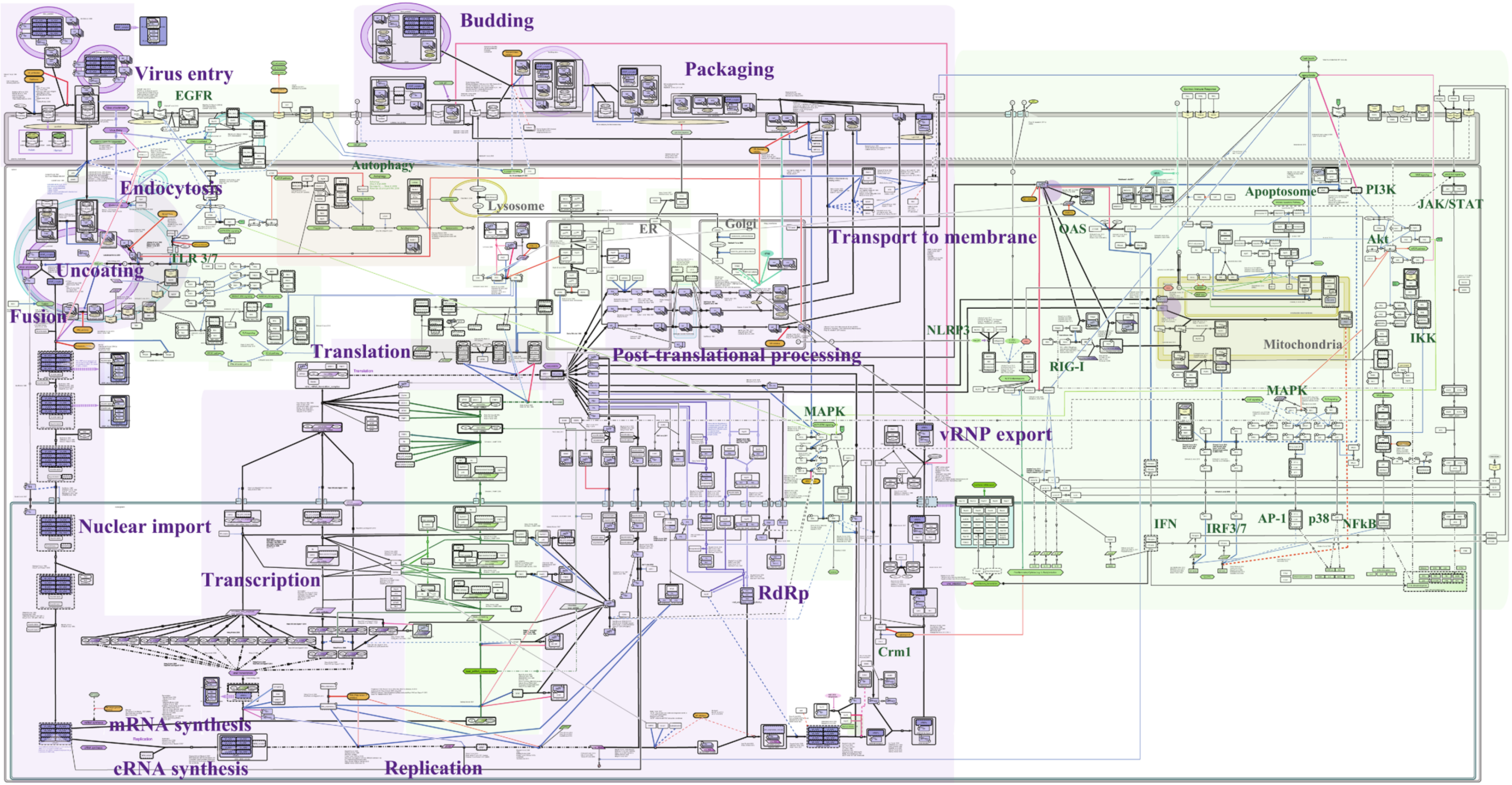
# The influenza virus replication cycle



# The influenza virus replication cycle



# The influenza virus replication cycle




***Virus-host interactions determine replication efficiency, transmission, disease***

Flu Map
http://www.influenza-x.org/flumap/
Matsuoka *et al.* (2013)

# Genome-wide screens to identify host factors



~20,000 human genes

## 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)

## 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, ACRC, ACSL1, ACSL4, ACTC1, ACTL6B, ACTN2, ACVR1C, ACVR2A, ADAM8, ADAMTS1, ADAMTS2, ADAMTSL4, ADAT1, ADCY7, ADRA1B, ADRB2, ADRBK2, AFF2, AGTRAP, AHCY, AHCYL1, AHNAK2, AHR, AIG1, AKAP11, AKAP13, AKT1, AKT3, ALAS1,
ALG10, ALG6, ALPK2, AMHR2, AMMECR1, AMN, AMOTL1, AMOTL2, ANAPC2, ANGPTL3, ANKK1, ANKMY2, ANKRD7, ANKS6, ANPEP, AP2B1, AP2M1, APBA3, APBB1IP, APC, APC2, APOA1, APOA5, APOBEC3G, APOL6, APP, APPBP1, AQP4, AQR, ARAF, ARCN1, ARD1, ARL4A, ARMCX5, ARNT, ARTN, ASAH1, ASPA, ATCAY, ATF1,
ATF2, ATF4, ATG16L1, ATP13A1, ATP1A2, ATP1A3, ATP2C1, ATP5B, ATP5C1, ATP5F1, ATP5I, ATP6AP1, ATP6AP2, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V0E2, ATP6V1A, ATP6V1B2, ATP6V1G1, ATP8, AXIN1, B2M, B3GALT2, B3GNT7, B4GALT2, BACE1, BACH2, BAIAP2, BAIAP3, BANP, BARHL2, BCAS2, BCL10, BCL3, BCR, BHLHB2,
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ATP5L, ATP5O, ATP6V1H, ATRIP, ATRN, ATXN10, ATXN7L3B, AUP1, B4GALT1, B4GALT4, BAG2, BAG3, BAG4, BAG5, BASP1, BAT1, BIRC6, BOP1, BRAT1, BRD8, BRSK1, BTAF1, BUB3, BYSL, BZW1, C14orf156, C14orf166, C16orf80, C17orf85, C18orf34, C19orf43, C19orf52, C20orf114, C6orf211, C7orf27, C7ORF50, C8orf33,
C9ORF167, CA12, CAD, CALR, CALU, CAND1, CANX, CAPN1, CAPNS1, CAPRIN1, CAPZA1, CAPZA2, CAPZB, CASC3, CBX3, CCAR2, CCDC135, CCDC42, CCDC47, CCDC56, CCDC88C, CCHCHD4, CCT1, CCT2, CCT3, CCT4, CCT5, CCT6A, CCT7, CCT8, CD59, CD97, CDC123, CDC2, CDC23, CDC42, CDC42EP1, CDK13, CDK2AP1,
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COPG2, COPS7A, COPS7B, CORO1C, COX11, COX15, COX5A, CPS1, CPSF1, CPSF2, CPSF3, CPSF7, CPT1A, CRTAP, CRYAB, CSE1L, CSNK2A1, CSNK2B, CSRP1, CSTF1, CSTF2, CSTF3, CTBP1, CTBP2, CTCF, CTNNA1, CTNNAL1, CTNNB1, CTNND1, CTPS1, CTSB, CTSD, CTTN, CUL4A, CYB5B, CYBA, CYC1, CYFIP2, CYP24A1, CYR61,
DAP3, DARS, DARS2, DBI, DBT, DCAF8, DDA1, DDB1, DDOST, DDX1, DDX10, DDX17, DDX18, DDX21, DDX24, DDX3, DDX39, DDX39A, DDX39B, DDX3X, DDX3Y, DDX41, DDX5, DDX55, DDX57, DECR1, DGCR14, DHCR7, DHX15, DHX30, DHX36, DHX38, DHX8, DICER1, DIMT1, DKC1, DKFZP564J0863, DLST, DNAJA1, DNAJA2,
DNAJA3, DNAJB1, DNAJB11, DNAJB12, DNAJB2, DNAJB6, DNAJC11, DNAJC3, DNAJC7, DNAJC9, DNM1, DNM1L, DNM2, DNMT1, DOCK5, DPM1, DPM3, DPY30, DPYSL2, DSG2, DSTN, DYNC1H1, DYNC1LI1, DYNC1LI2, DYNLL1, E2F7, ECD, ECH1, ECM29, EDC4, EDEM3, EEF1A2, EEF1E1, EEF1G, EEF2, EFR3A, EFTUD2, EGFR,
EHD1, EHD2, EHD3, EHD4, EIF3A, EIF3B, EIF3CL, EIF3D, EIF3E, EIF3F, EIF3H, EIF3I, EIF4A1, EIF4A3, EIF4B, EIF4E, EIF4G1, EIF4G2, EIF4G3, EIF5, EIF5A, EIF6, EMD, eno1, EPHA2, EPRS, ERAL1, ERAP1, ERCC6L, ERGIC1, ERH, ERLIN1, ERLIN2, ESYT1, ETAA1, ETFA, EWSR1, EXOC2, EXOC4, EXOC5, EXOC6, EXOC7, EZR, FADS1, FADS2,
FAF2, FAM120A, FAM120C, FAM129B, FAM3A, FAM62B, FAM73B, FAM83H, FAM98A, FANCD2, FANCI, FAR1, FARP1, FARSA, FASN, FASTKD5, FAU, FBLN1, FBXO2, FDFT1, FGG, FH, FHOD1, FIP1L1, FITM2, FKBP8, FLII, FLNB, FLVCR1, FMR1, FOCAD, FRAP1, FUBP1, FUS, FUT4, FXR2, G3BP2, G6PD, GALK1, GANAB, GAPDH, GAR1,
GARS, GART, GBF1, GCN1L1, GDI1, GDI2, GEMIN4, GEMIN5, GFPT1, ggt1, GLRX3, GLS, GLUD1, GNAI2, GNAS, GNB1, GNB2, GNB2L1, GNPAT, GOLPH3, GOSR1, GPC1, gpc4, GPRASP2, GPS1, GPSN2, GRAMD1A, GRPEL1, GTF2I, GTF3C5, H1FX, H3F3B, HADHB, HAUS6, HAX1, HDAC1, HDAC2, HEATR1, HEATR2, HEATR5A, HEATR6,
HECTD1, HELLS, HERC1, HEXIM1, HIGD1A, HIGD2A, HIST1H2BG, HIST1H3A; HIST1H3B; HIST1H3C; HIST1H3D; HIST1H3E; HIST1H3F; HIST1H3G; HIST1H3H; HIST1H3I; HIST1H3J, HIST2H3A; HIST2H3C; HIST2H3D, HIST2H3PS2, HKDC1, HLA B, HLTF, HMGN2, HMOX1, HNRNPA0, HNRNPA1, HNRNPA2B1, HNRNPD, HNRNPDL,
HNRNPH1, HNRNPK, hnrnpm, HNRNPR, HNRNPUL1, HNRNPUL2, HNRPM, HPS6, HSBP1, HSD17B11, HSD17B12, HSP90AA1, HSP90AB1, HSP90B1, HSPA1B, HSPA1L, HSPA2, HSPA4, HSPA4L, HSPA8, HSPA9, Hspb1, HSPBP1, HSPD1, HSPH1, HTATIP2, HTATSF1, HUWE1, HYOU1, IARS, ICMT, IDH3B, IGF2BP1, IGF2BP2, IGF2BP3,
IKBKAP, ILF2, ILF3, ILVBL, IMMT, IMPA2, IMPDH2, INF2, INTS1, INTS2, IPO11, IPO4, IPO5, IPO7, IPO9, IQGAP1, IQGAP2, IQSEC1, IRAK1, IRS4, ITGA3, Itgb1, ITGB5, ITM2B, ITPRIP, JAK1, JTV1, JUP, KARS, KCTD17, KCTD5, KDELR1, KDELR2, KHSRP, KIAA0368, KIAA0391, KIAA0406, KIAA0664, KIAA0776, KIAA0859, KIAA1279, KIF11,
KIF5B, KLC1, KNR3C1, KPNA1, KPNA2, KPNA3, KPNA4, KPNA6, KPNB1, KRT14, KRT18, KRT6B, KRT7, LAMA5, LAMB1, LANCL1, LARP1, LARP4B, LARS, LASP1, LBR, LDLR, LENG4, LETM1, LGALS1, LGALS3, LGALS3BP, LMNA, LMNB1, LONP1, LPCAT1, LPCAT4, LPGAT1, LRPPRC, LRRC40, LRRC59, LTV1, LUC7L, LUC7L3, LYCAT, MACF1,
MAD2L1, MAGED1, MAGED2, MAGED4, MAGT1, MAN1B1, MAP1B, MAP2K2, MAP2K3, MAP2K4, MAP7, MARS, MASTL, MAT2A, MATR3, MBNL1, MCM3, MCM5, MCM7, MCU, MDN1, MFN1, MGST1, MICU2, MLF2, MLLT11, MLSTD2, MMS19, MON2, MORC3, MOV10, MRFAP1, MRM1, MRPL1, MRPL10, MRPL12, MRPL13, MRPL15,
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MSH2, MSH6, MSI2, MT CO2, MTA2, MTCH1, MTCH2, MTDH, MTHFD1, MTHFD1L, MTR, MTUS1, MTX1, MVP, MX1, MYBBP1A, MYEF2, MYH10, MYH9, MYL12A, MYL6, MYO1B, MYO1C, MYOF, NA, NACA, NAP1L1, NAP1L4, NCAPD2, NCAPD3, NCAPG, NCBP1, NCBP2, NCKAP1L, NCL, NCLN, NCOA5, NDUFA10, NDUFA13, NDUFA4,
NDUFA5, NDUFA8, NDUFA9, NDUFAF4, NDUFS1, NDUFS2, NDUFS3, NDUFS8, NELFCD, NFIA, NGDN, NGLY1, NHP2L1, NIPSNAP1, NLRP2, NLRX1, NME2, NNMT, NNT, NOC2L, NOC4L, NOLC1, NONO, NOP10, NOP14, NOP56, NOP58, NOP9, NPM1, NQO1, NR3C1, NRAS, NSF, NSUN2, NT5C2, NTPCR, NUDC, NUP107, NUP133,
NUP153, NUP160, NUP188, NUP205, NUP210, NUP35, NUP85, NUP93, NUP98, OAT, OCIAD2, ODR4, OPA1, OSBPL5, OSMR, OXA1L, OXSR1, P4HA1, P4HB, PABPC1, PAF1, PARP1, PARP14, PARP4, PCBP2, PCDHB12, PCK2, PCMT1, PCNA, PDCD6, PDCD6IP, PDE3A, PDHB, PDIA3, PDIA4, PDIA6, PDLIM5, PDS5A, PDXDC1, PELO,
PES1, PEX19, PFDN2, PFDN6, PFKFB3, PFKL, PFKM, PFKP, pfn1, PGAM5, PGD, PGK1, PGRMC1, PGRMC2, PHB, PHB2, PHF5A, PHGDH, PJA2, PKM, PKM2, PKP3, PLAA, PLD3, PLEC, PLIN2, PLIN3, PLOD1, PLOD2, PLOD3, PLXNB2, PNN, PNPLA2, PNPLA6, POLDIP2, POLE4, POLR1A, POLR1C, POLR2A, POLR2B, POLR2C, POLR2D,
POLR2E, POLR2G, POLR2H, POLR2I, POLR2J, POLR2L, PON2, PPA1, PPIAL3, PPIB, PPM1B, PPM1G, PPP1CA, PPP1CB, PPP1CC, PPP2CA, PPP2R1A, PPP2R2A, PPP6C, PPP6R1, PPP6R3, PRC1, PRDX1, PRDX3, PRDX4, PRDX6, PRKACA, PRKACB, PRKAR1A, PRKCSH, PRKDC, PRMT1, PRMT5, PRPF40A, PRPF6, PRPF8, PRPS1, PRPSAP1,
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RDH11, RETSAT, RFC3, RHOF, RHOG, RHOT1, RHOT2, RHPN2, RIC8A, RICTOR, RNF149, RNF213, RNF219, RNH1, RPL10A, RPL10L, RPL11, RPL15, RPL17, RPL18, RPL18A, RPL21, RPL22, RPL24, RPL26, RPL27A, RPL3, RPL30, RPL34, RPL35A, RPL36, RPL5, RPL7L1, RPL9, RPLP0, RPLP2, RPN1, RPN2, RPRD1B, RPS10, RPS12, RPS13,
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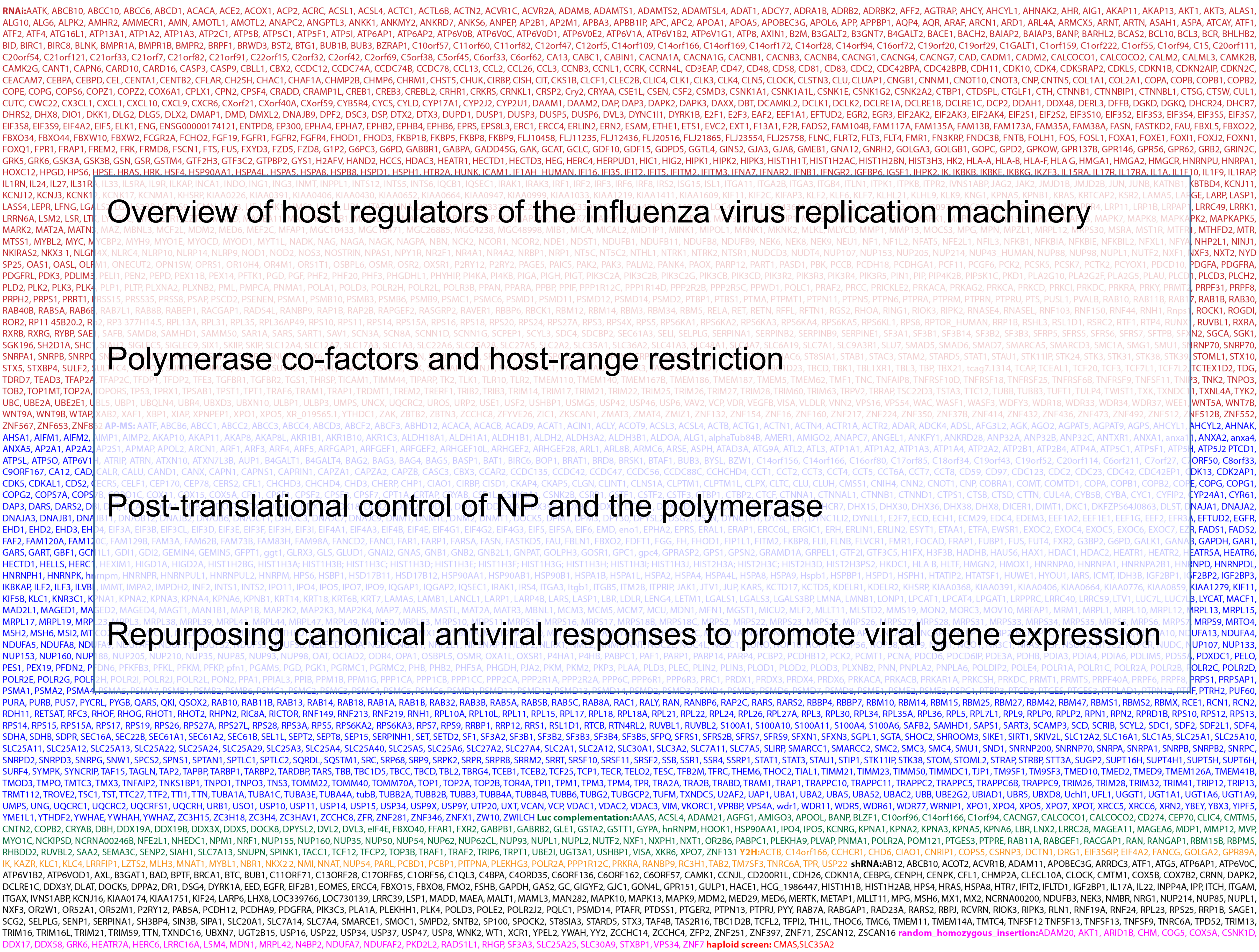
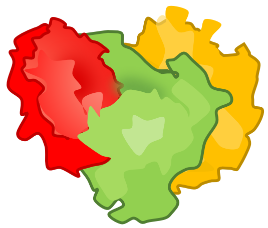
SDHA, SDHB, SDPR, SEC16A, SEC22B, SEC61A1, SEC61A2, SEC61B, SEL1L, SEPT2, SEPT8, SEP15, SERPINH1, SET, SETD2, SF1, SF3A2, SF3B1, SF3B2, SF3B3, SF3B4, SF3B5, SFPQ, SFRS1, SFRS2B, SFRS7, SFRS9, SFXN1, SFXN3, SGPL1, SGTA, SHOC2, SHROOM3, SIKE1, SIRT1, SKIV2L, SLC12A2, SLC16A1, SLC1A5, SLC25A1, SLC25A10,
SLC25A11, SLC25A12, SLC25A13, SLC25A22, SLC25A24, SLC25A29, SLC25A3, SLC25A4, SLC25A40, SLC25A5, SLC25A6, SLC27A2, SLC27A4, SLC2A1, SLC2A12, SLC30A1, SLC3A2, SLC7A11, SLC7A5, SLIRP, SMARCC1, SMARCC2, SMC2, SMC3, SMC4, SMU1, SND1, SNRNP200, SNRNP70, SNRPA, SNRPA1, SNRPB, SNRPB2, SNRPC,
SNRPD2, SNRPD3, SNRPG, SNW1, SPCS2, SPNS1, SPTAN1, SPTLC1, SPTLC2, SQRDL, SQSTM1, SRC, SRP68, SRP9, SRPK2, SRPR, SRPRB, SRRM2, SRRT, SRSF10, SRSF11, SRSF2, SSB, SSR1, SSR4, SSRP1, STAT1, STAT3, STAU1, STIP1, STK11IP, STK38, STOM, STOML2, STRAP, STRBP, STT3A, SUGP2, SUPT16H, SUPT4H1, SUPT5H, SUPT6H,
SURF4, SYMPK, SYNCRIP, TAF15, TAGLN, TAP2, TAPBP, TARBP1, TARBP2, TARDBP, TARS, TBB, TBC1D5, TBCC, TBCD, TBL2, TBRG4, TCEB1, TCEB2, TCF25, TCP1, TECR, TELO2, TESC, TFB2M, TFRC, THEM6, THOC2, TIAL1, TIMM21, TIMM23, TIMM50, TIMMDC1, TJP1, TM9SF1, TM9SF3, TMED10, TMED2, TMED9, TMEM126A, TMEM41B,
TMOD3, TMPO, TMTC3, TMX3, TNFAIP2, TNKS1BP1, TNPO1, TNPO3, TNS3, TOMM22, TOMM40, TOMM70A, TOP1, TOP2A, TOP2B, TOR4A, TPI1, TPM1, TPM3, TPM4, TPR, TRA2A, TRA2B, TRABD, TRAM1, TRAP1, TRAPPC10, TRAPPC11, TRAPPC2, TRAPPC5, TRAPPC6B, TRAPPC9, TRIM26, TRIM28, TRIM32, TRIM41, TRIP12, TRIP13,
TRMT112, TROVE2, TSC1, TST, TTC27, TTF2, TTI1, TTN, TUBA1A, TUBA1C, TUBA3E, TUBA4A, tubB, TUBB2A, TUBB2B, TUBB3, TUBB4A, TUBB4B, TUBB6, TUBG2, TUBGCP2, TUFM, TXNDC5, U2AF2, UAP1, UBA1, UBA2, UBA5, UBA52, UBAC2, UBB, UBE2G2, UBIAD1, UBR5, UBXD8, Uchl1, UFL1, UGGT1, UGT1A1, UGT1A6, UGT1A9,
UMPS, UNG, UQCRC1, UQCRC2, UQCRFS1, UQCRH, URB1, USO1, USP10, USP11, USP14, USP15, USP34, USP9X, USP9Y, UTP20, UXT, VCAN, VCP, VDAC1, VDAC2, VDAC3, VIM, VKORC1, VPRBP, VPS4A, wdr1, WDR11, WDR5, WDR61, WDR77, WRNIP1, XPO1, XPO4, XPO5, XPO7, XPOT, XRCC5, XRCC6, XRN2, YBEY, YBX3, YIPF5,
YME1L1, YTHDF2, YWHAE, YWHAH, YWHAZ, ZC3H15, ZC3H18, ZC3H4, ZC3HAV1, ZCCHC8, ZFR, ZNF281, ZNF346, ZNFX1, ZW10, ZWILCH **Luc complementation:**AAAS, ACSL4, ADAM21, AGFG1, AMIGO3, APOOL, BANP, BLZF1, C10orf96, C14orf166, C1orf94, CACNG7, CALCOCO1, CALCOCO2, CD274, CEP70, CLIC4, CMTM5,
CNTN2, COPB2, CRYAB, DBH, DDX19A, DDX19B, DDX3X, DDX5, DOCK8, DPYSL2, DVL2, DVL3, eIF4E, FBXO40, FFAR1, FXR2, GABPB1, GABRB2, GLE1, GSTA2, GSTT1, GYPA, hnRNPM, HOOK1, HSP90AA1, IPO4, IPO5, KCNRG, KPNA1, KPNA2, KPNA3, KPNA5, KPNA6, LBR, LNX2, LRRC28, MAGEA11, MAGEA6, MDP1, MMP12, MVP,
MYO1C, NCKIPSD, NCRNA00246B, NFE2L1, NHEDC1, NPM1, NRF1, NUP155, NUP160, NUP35, NUP50, NUP54, NUP62, NUP62CL, NUP93, NUPL1, NUPL2, NUTF2, NXF1, NXPH1, NXT1, OR2B6, PABPC1, PLEKHA9, PLVAP, PNMA1, POLR2A, POM121, PTGES3, PTPRE, RAB11A, RABGEF1, RACGAP1, RAN, RANGAP1, RBM15B, RBPMS,
RHBDD2, RUVBL2, SAA2, SEMA3C, SENP2, SIAH1, SLC7A13, SNUPN, SPINK1, TACC1, TCF12, TFCP2, TOP3B, TRAF1, TRAF2, TRIP6, TRPT1, UBE2I, UGT3A1, USHBP1, VISA, XKR6, XPO7, ZNF131 **Y2H:**ACTB, C14orf166, CCHCR1, CHD6, CIAO1, CNRIP1, COPS5, CSRNP3, DCTN1, DRG1, EIF3S6IP, EIF4A2, FANCG, GOLGA2, GPR89A,
IK, KAZR, KLC1, KLC4, LRRFIP1, LZTS2, MLH3, MNAT1, MYBL1, NBR1, NKX2 2, NMI, NNAT, NUP54, PARL, PCBD1, PCBP1, PITPNA, PLEKHG3, POLR2A, PPP1R12C, PRKRA, RANBP9, RC3H1, TAB2, TM7SF3, TNRC6A, TPR, USP22 **shRNA:**AB12, ABCB10, ACOT2, ACVR1B, ADAM11, APOBEC3G, ARRDC3, ATF1, ATG5, ATP6AP1, ATP6V0C,
ATP6V1B2, ATP6VOD1, AXL, B3GAT1, BAD, BPTF, BRCA1, BTC, BUB1, C11ORF71, C13ORF28, C17ORF85, C1ORF56, C1QL3, C4BPA, C4ORD35, C6ORF136, C6ORF162, C6ORF57, CAMK1, CCNJL, CD200R1L, CDH26, CDKN1A, CEBPG, CENPH, CENPK, CFL1, CHMP2A, CLECL10A, CLOCK, CMTM1, COX5B, COX7B2, CRNN, DAPK2,
DCLRE1C, DDX3Y, DLAT, DOCK5, DPPA2, DR1, DSG4, DYRK1A, EED, EGFR, EIF2B1, EOMES, ERCC4, FBXO15, FBXO8, FMO2, FSHB, GAPDH, GAS2, GC, GIGYF2, GJC1, GON4L, GPR151, GULP1, HACE1, HCG_1986447, HIST1H1B, HIST1H2AB, HPS4, HRAS, HSPA8, HTR7, IFIT2, IFLTD1, IGF2BP1, IL17A, IL22, INPP4A, IPP, ITCH, ITGAM,
ITGAX, IVNS1ABP, KCNJ16, KIAA0174, KIAA1751, KIF24, LARP6, LHX8, LOC339766, LOC730139, LRRC39, LSP1, MADD, MAEA, MALT1, MAML3, MAN282, MAPK10, MAPK13, MAPK9, MDM2, MED29, MED6, MERTK, METAP1, MLLT11, MPG, MSH6, MX1, MX2, NCRNA00200, NDUFB3, NEK3, NMBR, NRG1, NUP214, NUP85, NUPL1,
NXF3, OR2W1, OR52A1, OR52M1, P2RY12, PAB5A, PCDH12, PCDHA9, PDGFRA, PIK3C3, PLA1A, PLEKHH1, PLK4, POLD3, POLE2, POLR2J2, PQLC1, PSMD14, PTAFR, PTDSS1, PTGER2, PTPN13, PTPRJ, PYY, RAB7A, RABGAP1, RAD23A, RARS2, RBPJ, RCVRN, RIOK3, RIPK3, RLN1, RNF19A, RNF24, RPL23, RPS25, RRP1B, SAGE1,
SCG2, SELPLG, SENP1, SERPINA1, SH3BP4, SIN3B, SIPA1, SLC20A1, SLC7A14, SLC7A4, SMARCE1, SMOC1, SMPD2, SNTB2, SP100, SPOCK2, ST8SIA3, STARD5, STX3, TAF4B, TAS2R16, TBC1D2B, TCFL2, TFPI2, TH1L, THOC6, TMC6, TMEM11, TMEM14A, TMTC4, TNFSF12 TNFSF13, TNFSF13, TNFSF9, TNRC6A, TPD52, TRIM13,
TRIM16, TRIM16L, TRIM21, TRIM59, TTN, TXNDC16, UBXN7, UGT2B15, USP16, USP22, USP34, USP37, USP47, USP8, WNK2, WT1, XCR1, YPEL2, YWAH, YY2, ZCCHC14, ZCCHC4, ZFP2, ZNF251, ZNF397, ZNF71, ZSCAN12, ZSCAN16 **random_homozygous_insertion:**ADAM20, AKT1, ARID1B, CHM, COG5, COX5A, CSNK1D,
DDX17, DDX58, GRK6, HEATR7A, HERC6, LRRC16A, LSM4, MDN1, MRPL42, N4BP2, NDUFA7, NDUFAF2, PKD2L2, RAD51L1, RHGP, SF3A3, SLC25A25, SLC30A9, STXBP1, VPS34, ZNF7 **haploid screen:** CMAS,SLC35A2


Overview of host regulators of the influenza virus replication machinery
Polymerase co-factors and host-range restriction
Post-translational control of NP and the polymerase
Repurposing canonical antiviral responses to promote viral gene expression

# The influenza polymerase

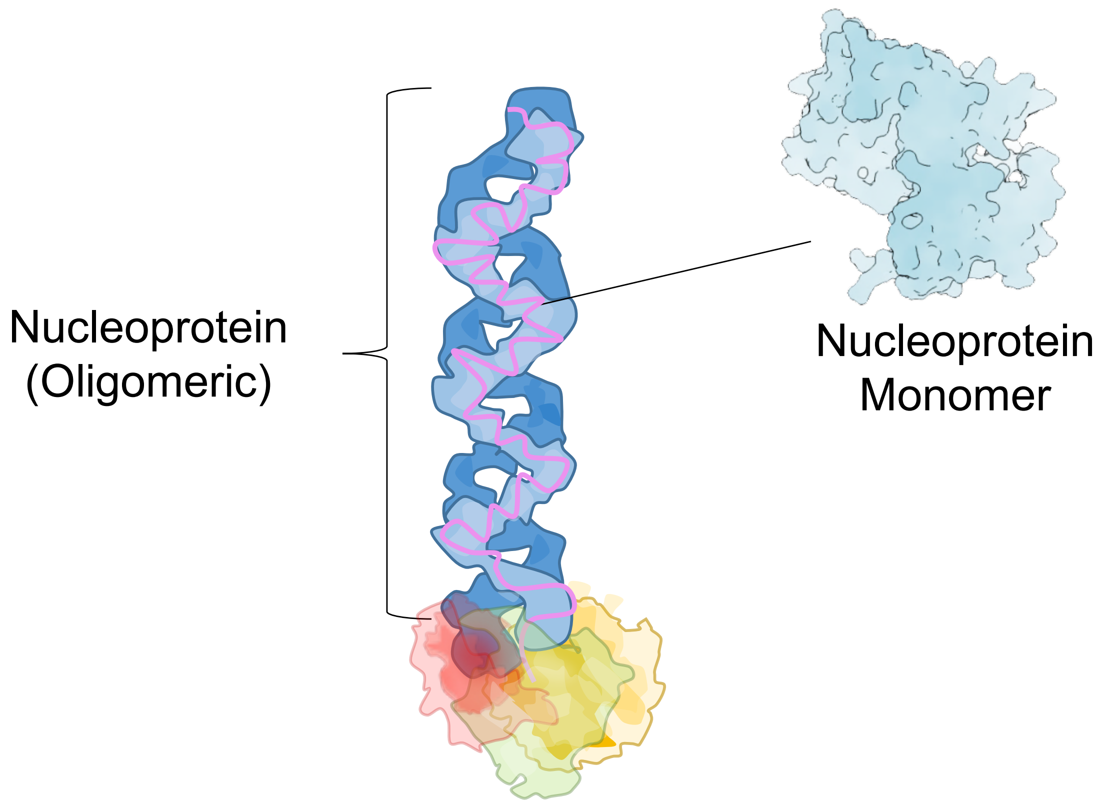
**PA:**
endonucleolytic
cleavage



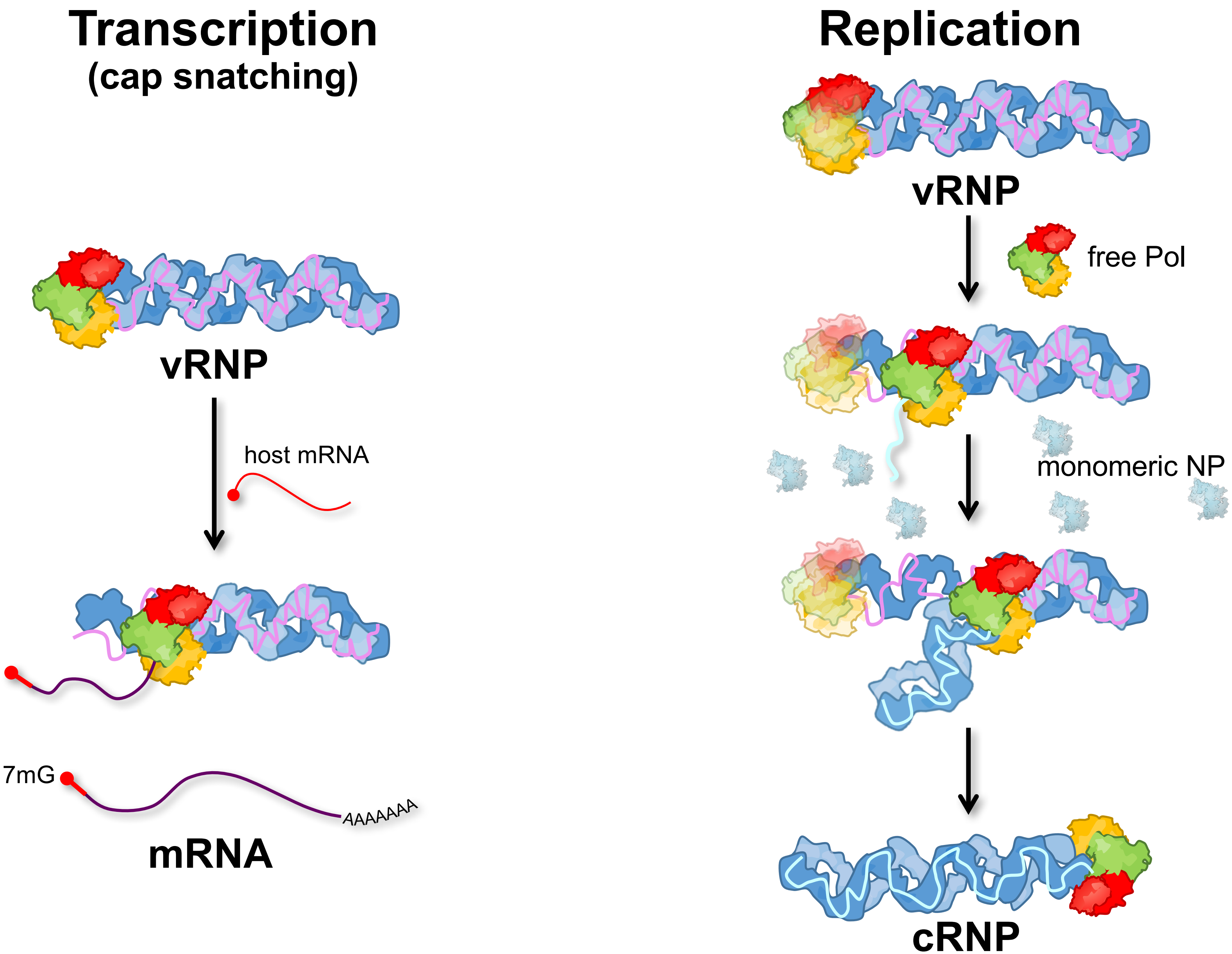
**PB2:**
binding of $^7$mG cap on mRNA

**PB1:**
5' + 3' RNA binding
polymerase activity

# The influenza RNP



# Regulated RNP assembly

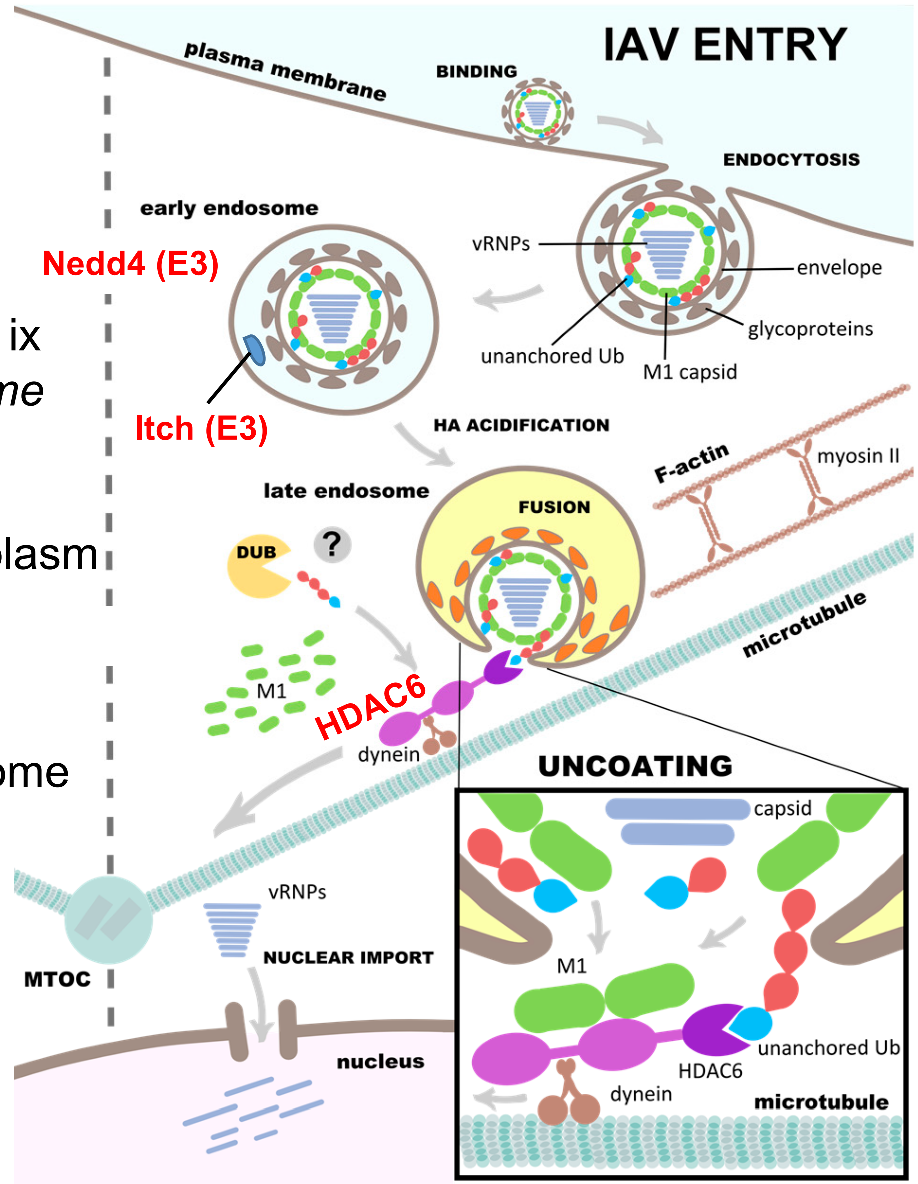


# Getting into nucleus: ubiquitin, Itch and HDAC6 facilitate uncoating

<u>Nedd4</u> – E3 Ub ligase
targets IFITM3
*enables release from endosome*

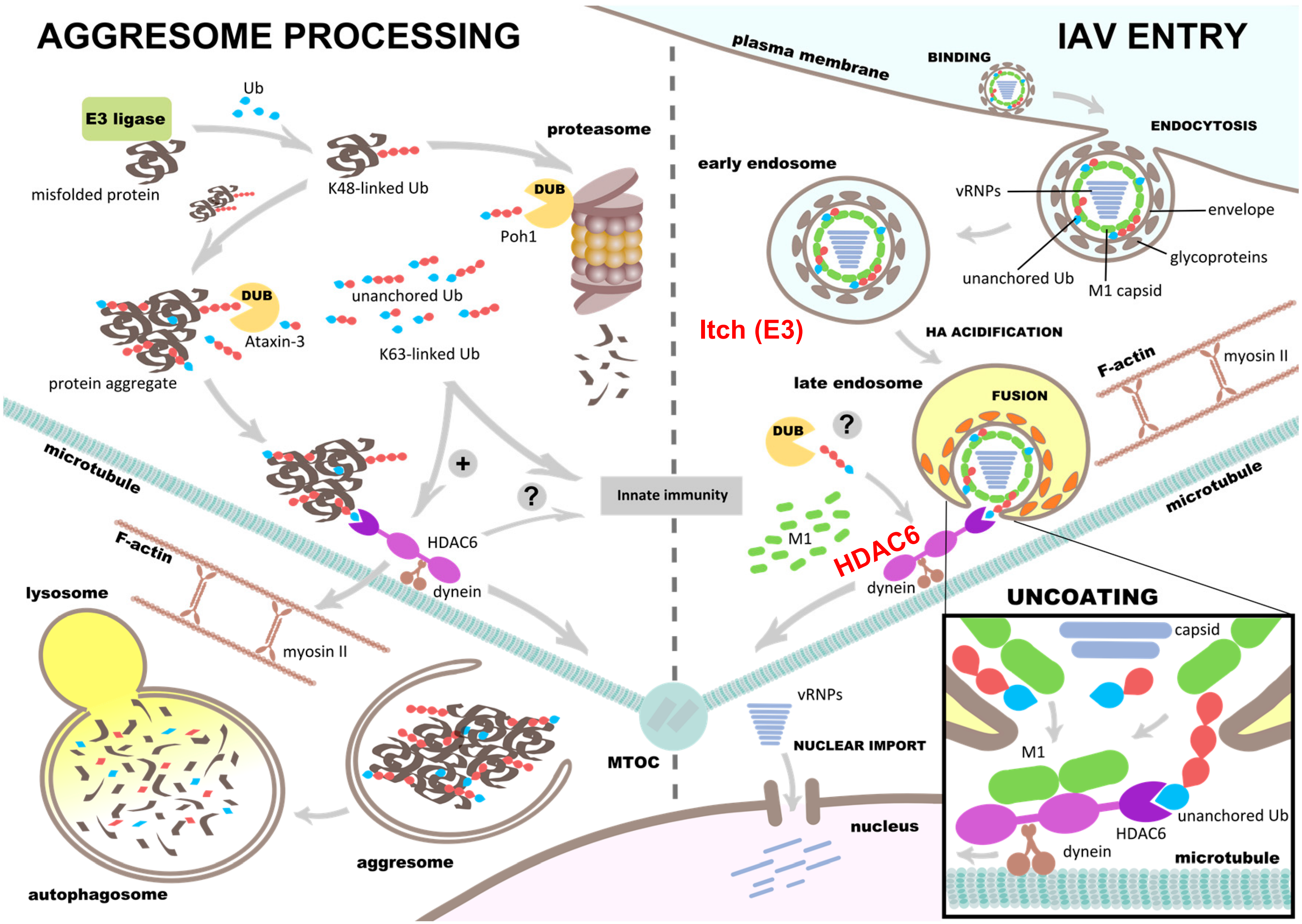
<u>Itch</u> – E3 Ub ligase
recruited inside endosome during ix
*helps release virion from endosome*
targets M1

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




Chesarino, 2015 PLoS Path; Su, 2013 PNAS; Banerjee 2014 Science; image from Rudanick and Yamauchi 2016 Viruses.

# Getting into nucleus: ubiquitin, Itch and HDAC6 facilitate uncoating




Chesarino, 2015 PLoS Path; Su, 2013 PNAS; Banerjee 2014 Science; image from Rudanick and Yamauchi 2016 Viruses.

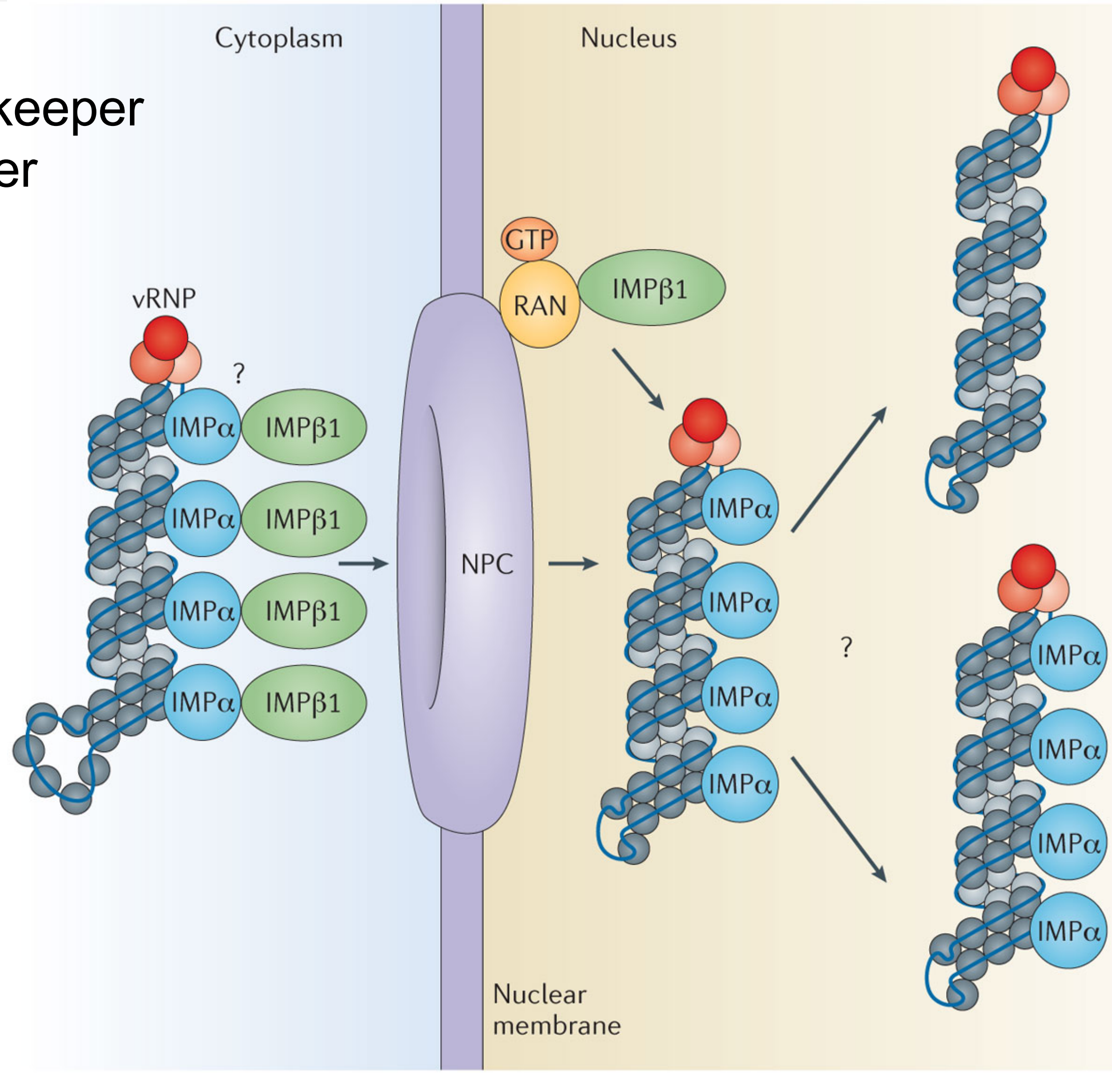
# Getting into nucleus: importance of importins

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

IMPα – adaptor, recognized NLS
IMPβ – transport receptor

Cargo:IMPα:IMPβ transit NPC

RAN dissociates and exports IMPβ
CSE1L dissociate IMPα from cargo



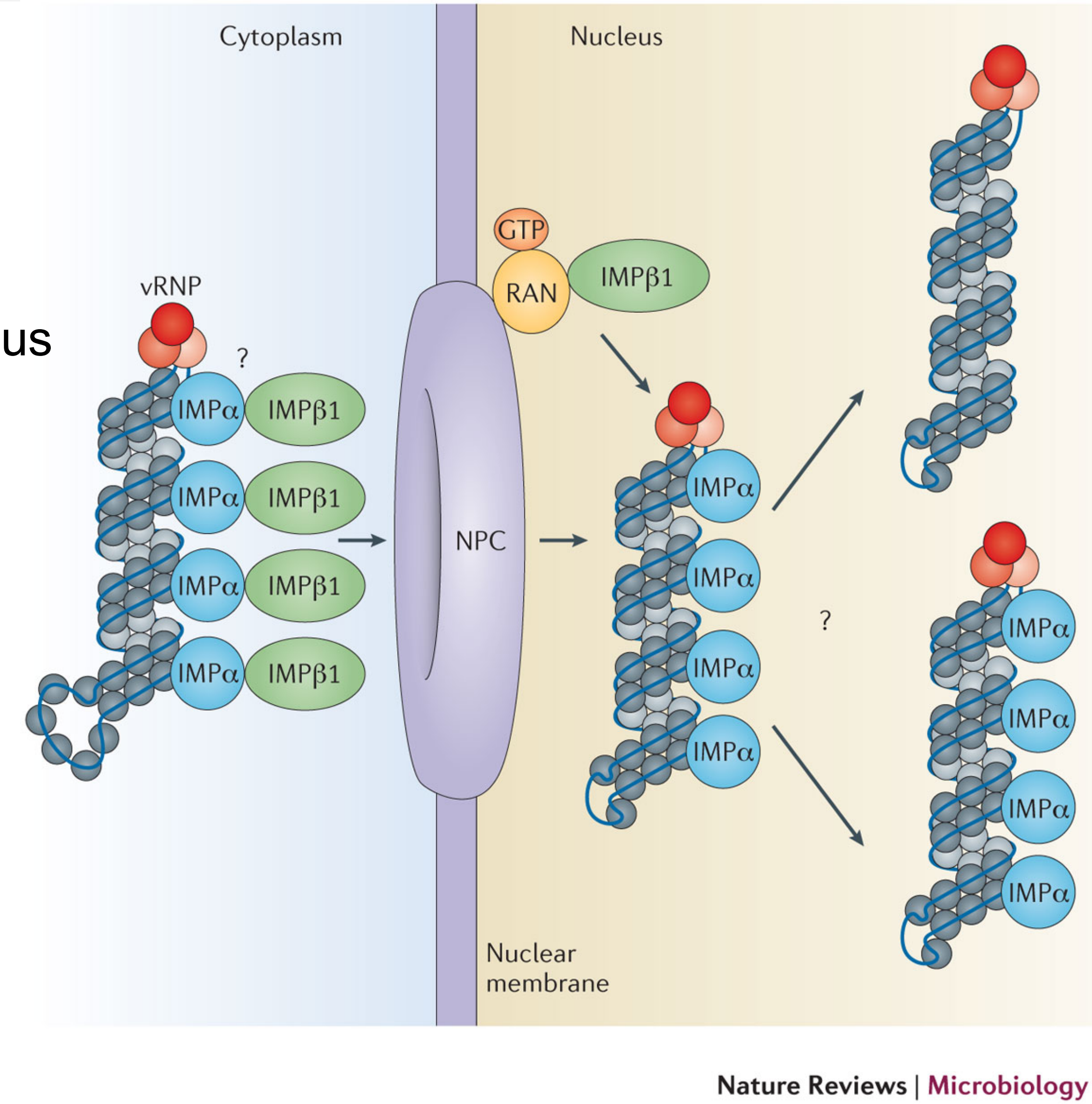

Nature Reviews | Microbiology

Eisfeld, et al. 2014 Nature Reviews Micro

# Getting into nucleus: importance of importins

PB2, PB1 and NP have well defined NLS

**NP:IMPα1- IMPβ1** or **NP:IMPα5-IMPβ1** thought to drive RNP to nucleus




Eisfeld, et al. 2014 Nature Reviews Micro

# Getting into nucleus: 8-segmented ride sharing?

PB2, PB1 and NP have well defined NLS

**NP:IMPα1- IMPβ1** or **NP:IMPα5-IMPβ1** thought to drive RNP to nucleus

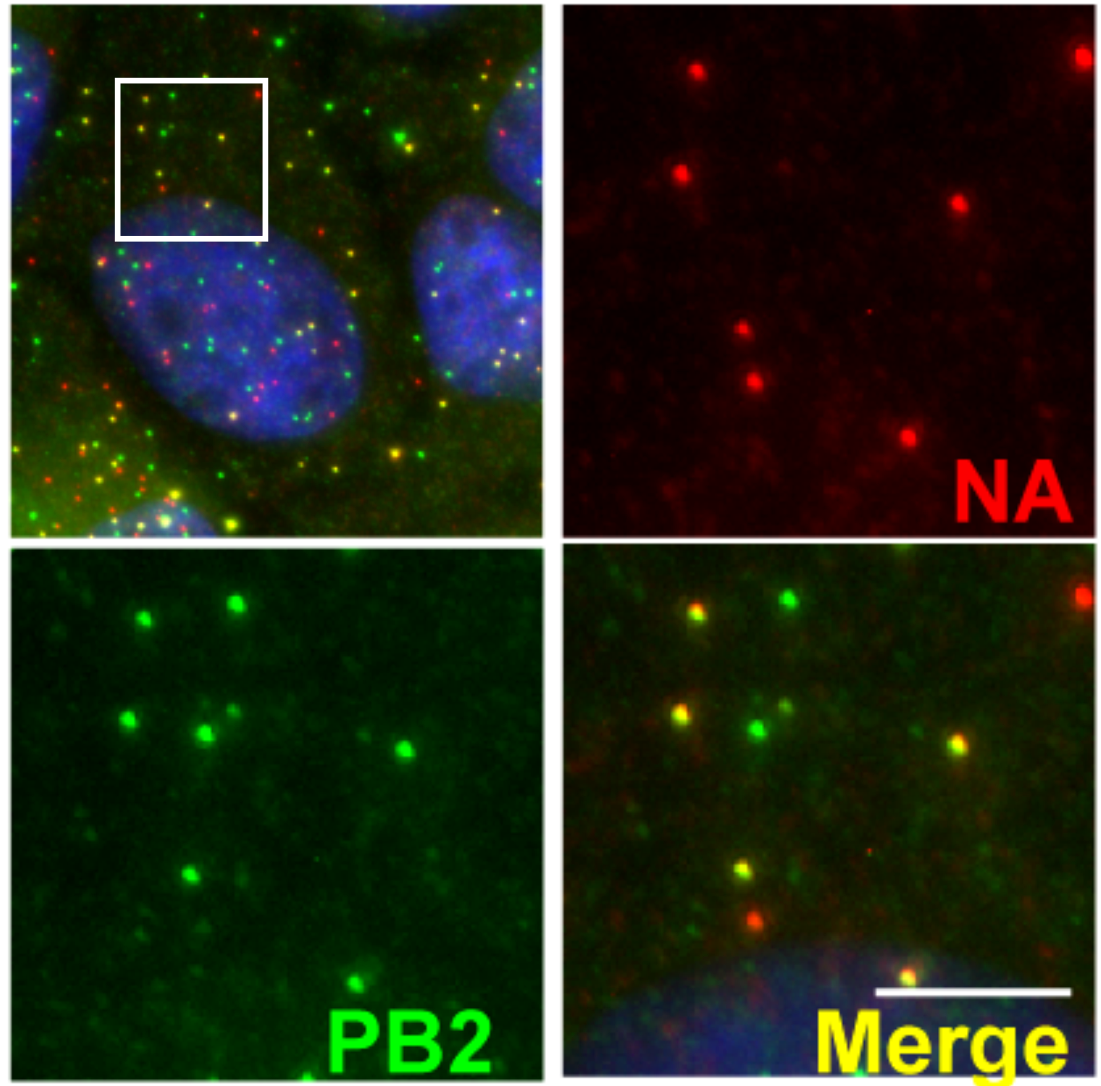
smFISH suggests incoming RNPs remain associated during import, and dissociate only after nuclear import (Chou, et al. 2013).

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

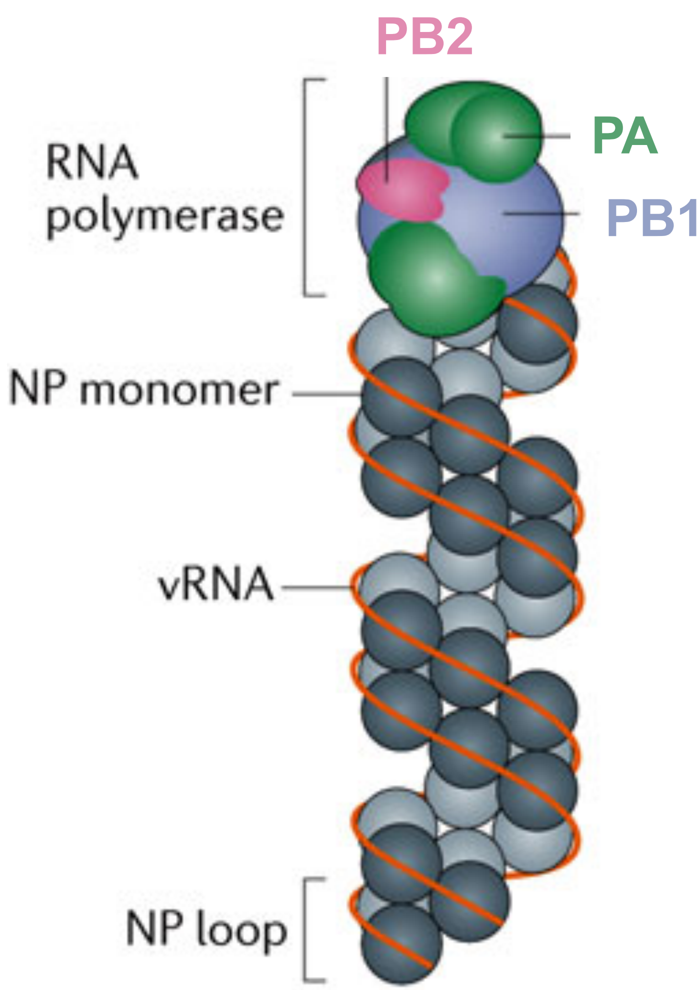
stained vRNA

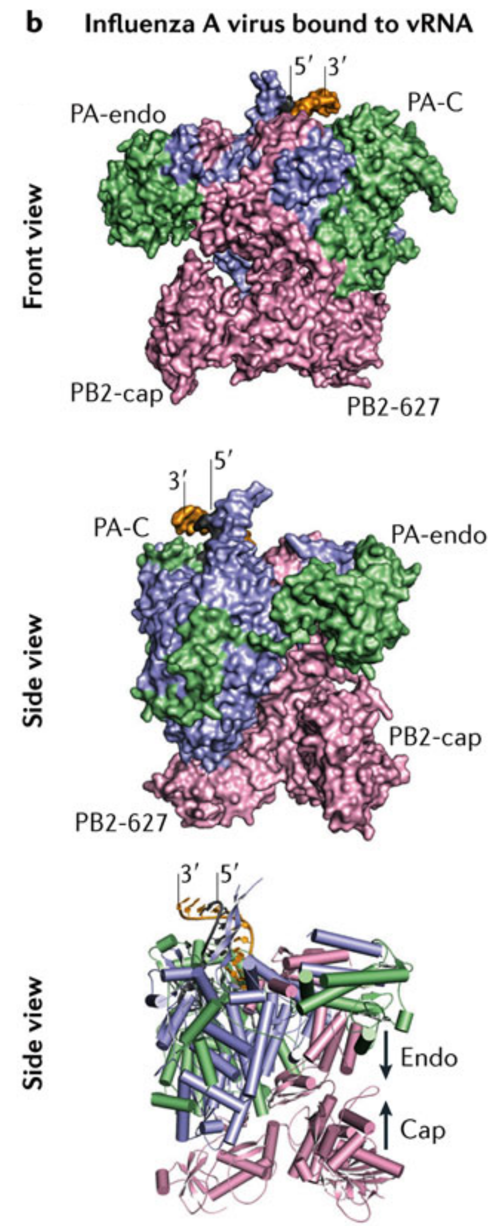



20m post-infection

Chou, et al. 2013 PLoS Pth

# Conformational control of polymerase function

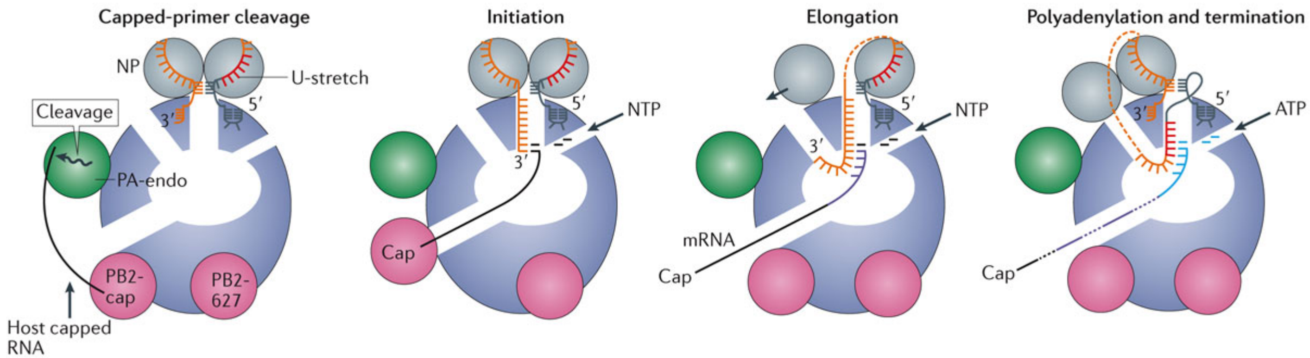



Te Velthuis & Fodor 2016
doi:10.1038/nrmicro.2016.87

# Conformational control of polymerase function

mRNA

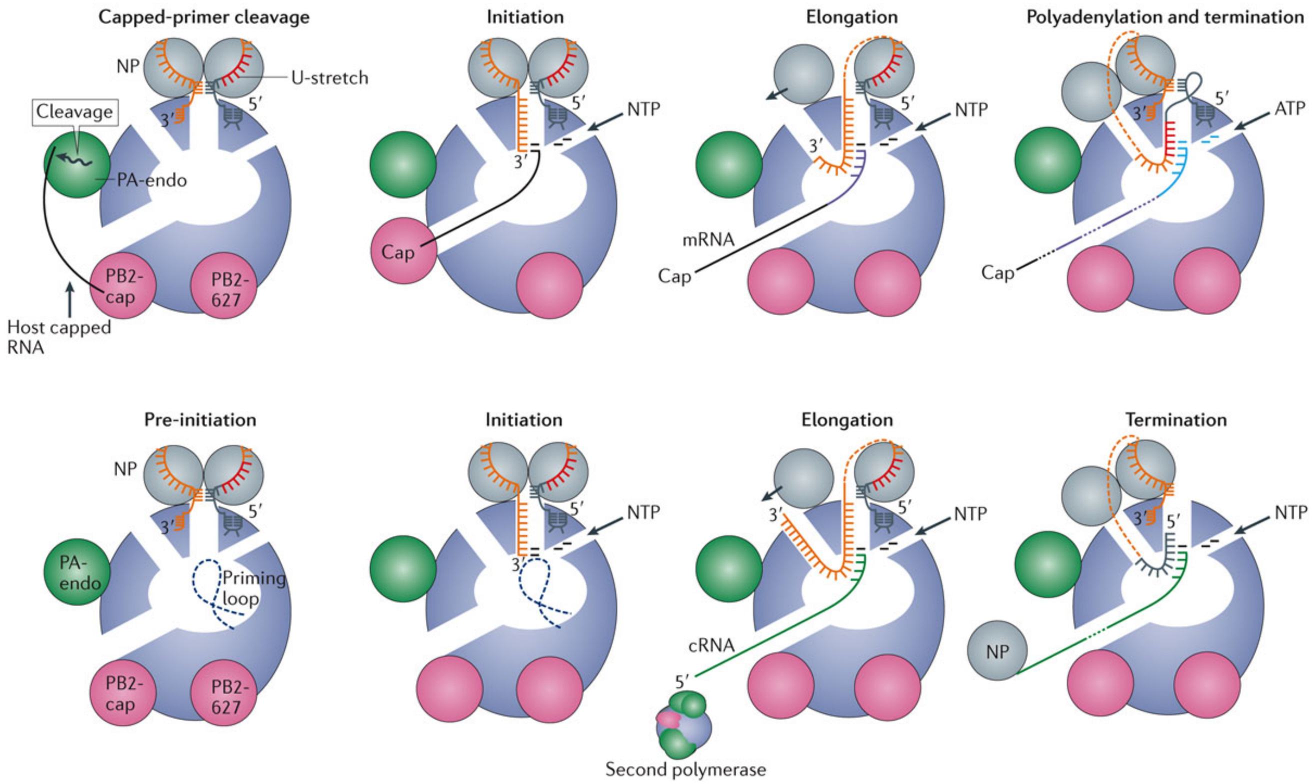



PB2-cap↔PA-endo
capped-primer

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

# Conformational control of polymerase function

mRNA




PB2-cap↔PA-endo capped-primer

cRNA

primer-independent priming loop

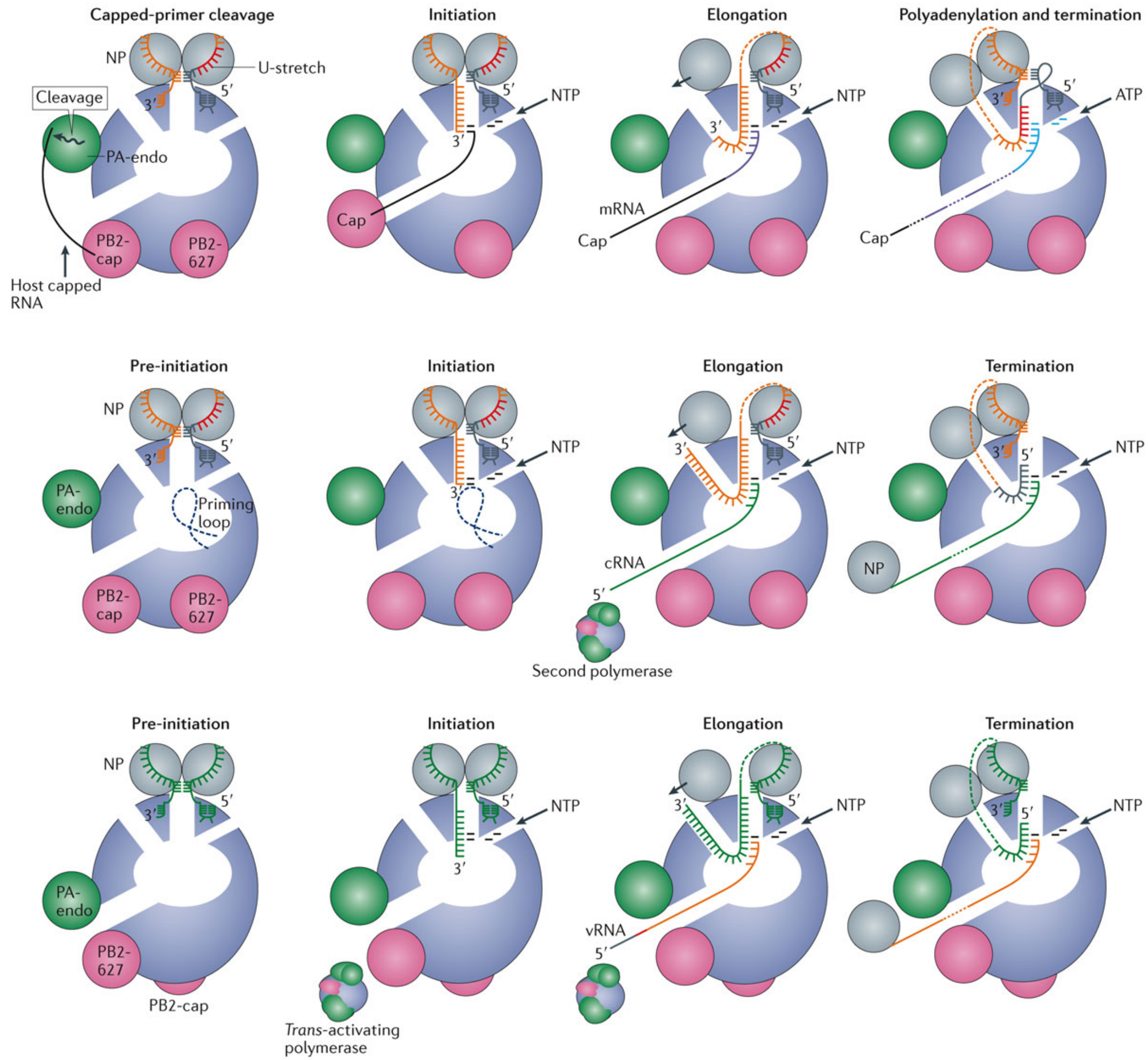
te Velthuis & Fodor 2016 doi:10.1038/nrmicro.2016.87

# Conformational control of polymerase function

mRNA

cRNA

vRNA




PB2-cap↔PA-endo
capped-primer

primer-independent
priming loop

primer-independent
prime-realign
*trans* activating
polymerase

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

# Cap-snatching co-factors

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

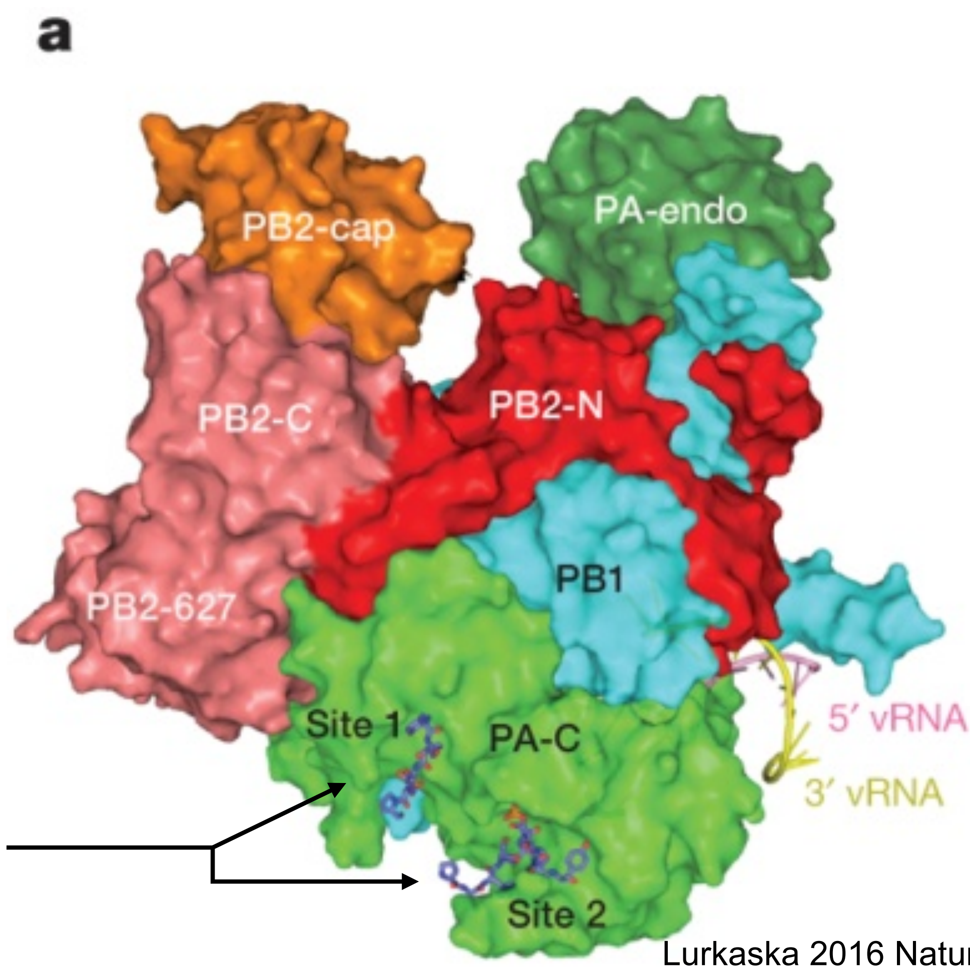
Influenza polymerase binds host pol II via pol II C-terminal domain (CTD), which encodes up to 52 repeats of $YS_2PTS_5PS$.

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*

Lurkaska 2016 Nature

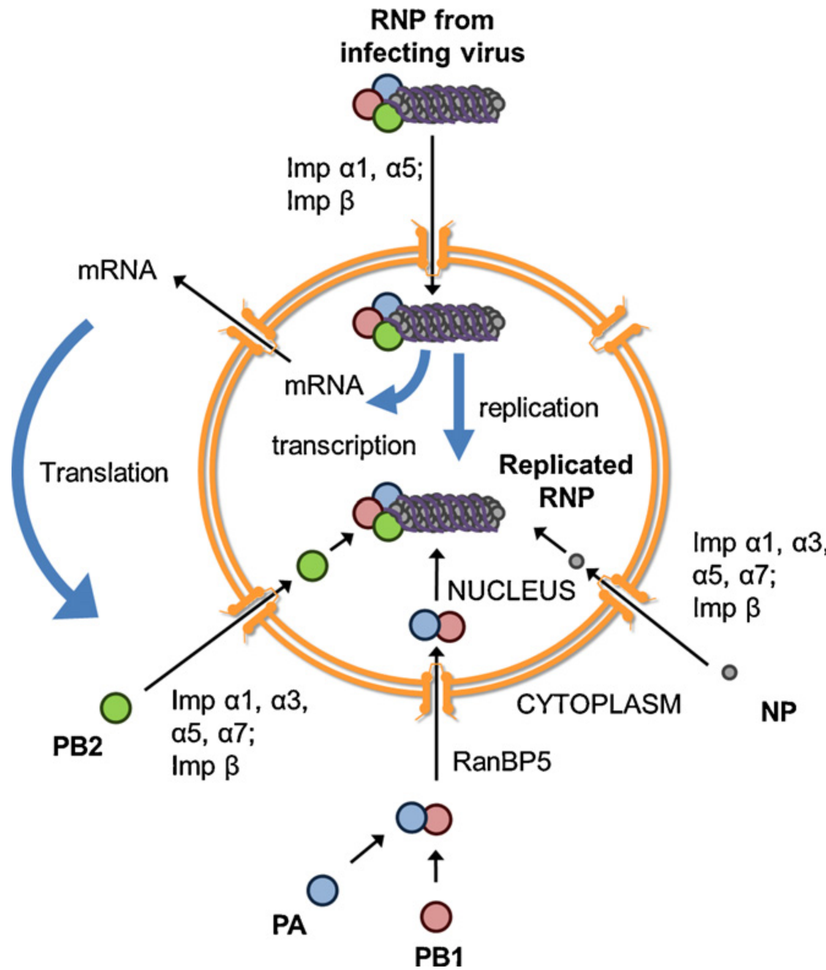
# Nuclear import and assembly of polymerase and NP

**PB2** and **NP**– Which IMPα is used? Redundant?

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

RanBP5 (IMPβ3) – non-classical import factor, directly engages NPC

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

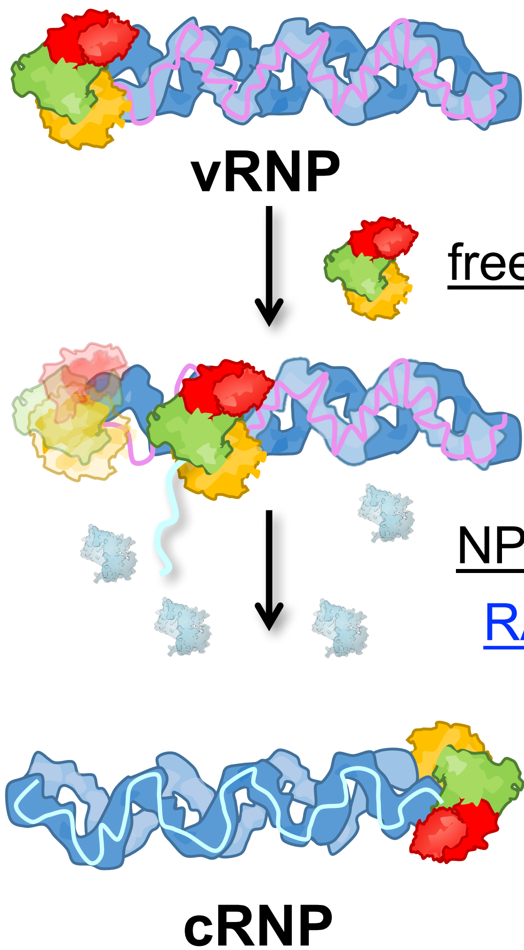



Hutchinson & Fodor 2012 Vaccine

**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
IMPα – suggest role post-import to stabilize assembly intermediates

# Factors directing vRNA → cRNA synthesis




NEP – biases vRNP towards cRNA synthesis

free Pol – becomes part of RNP

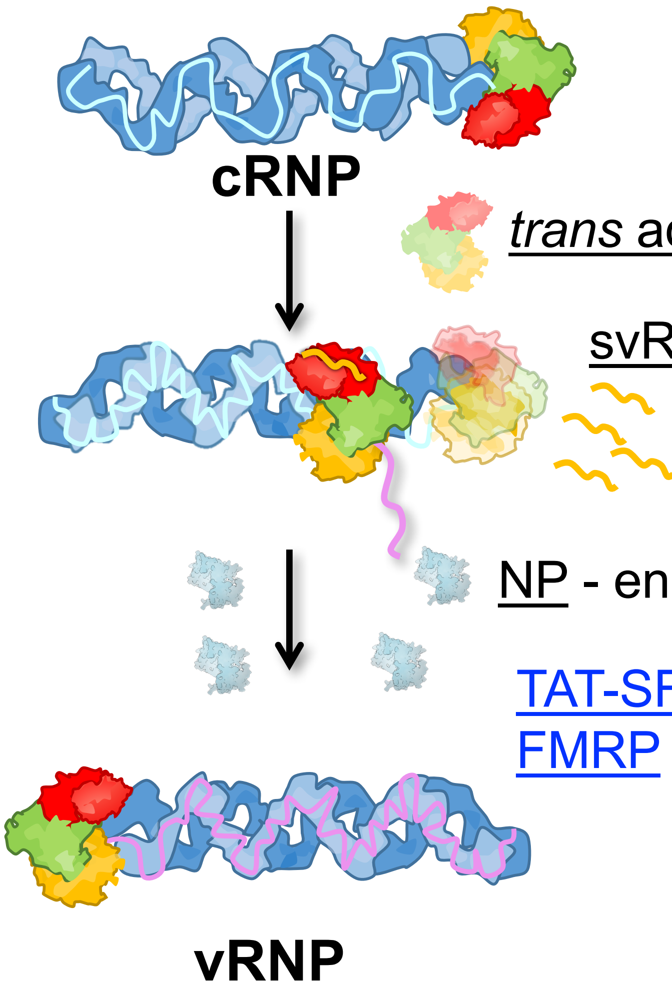
MCM2-7 – DNA helicase, binds PA. Enhances processivity.

NP - encapsidates cRNA

RAF-2p48 – recruits NP

viral in black, host in blue

# Factors directing cRNA → vRNA synthesis




<u>*trans* activating Pol</u> – stimulates RNP activity, catalytic?

<u>svRNA</u> – abortive vRNAs, bind to PA to promote elongation

<u>ANP32A/B</u> – bind trimeric Pol, full-length cRNA

<u>NP</u> - encapsidates vRNA

<u>TAT-SF1</u> – splicing factor, chaperones NP

<u>FMRP</u> – RNA binding protein, chaperones NP

viral in black, host in blue

# 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 recombindation/copy-choice occur?

How is NP loaded, and where?

# vRNP export

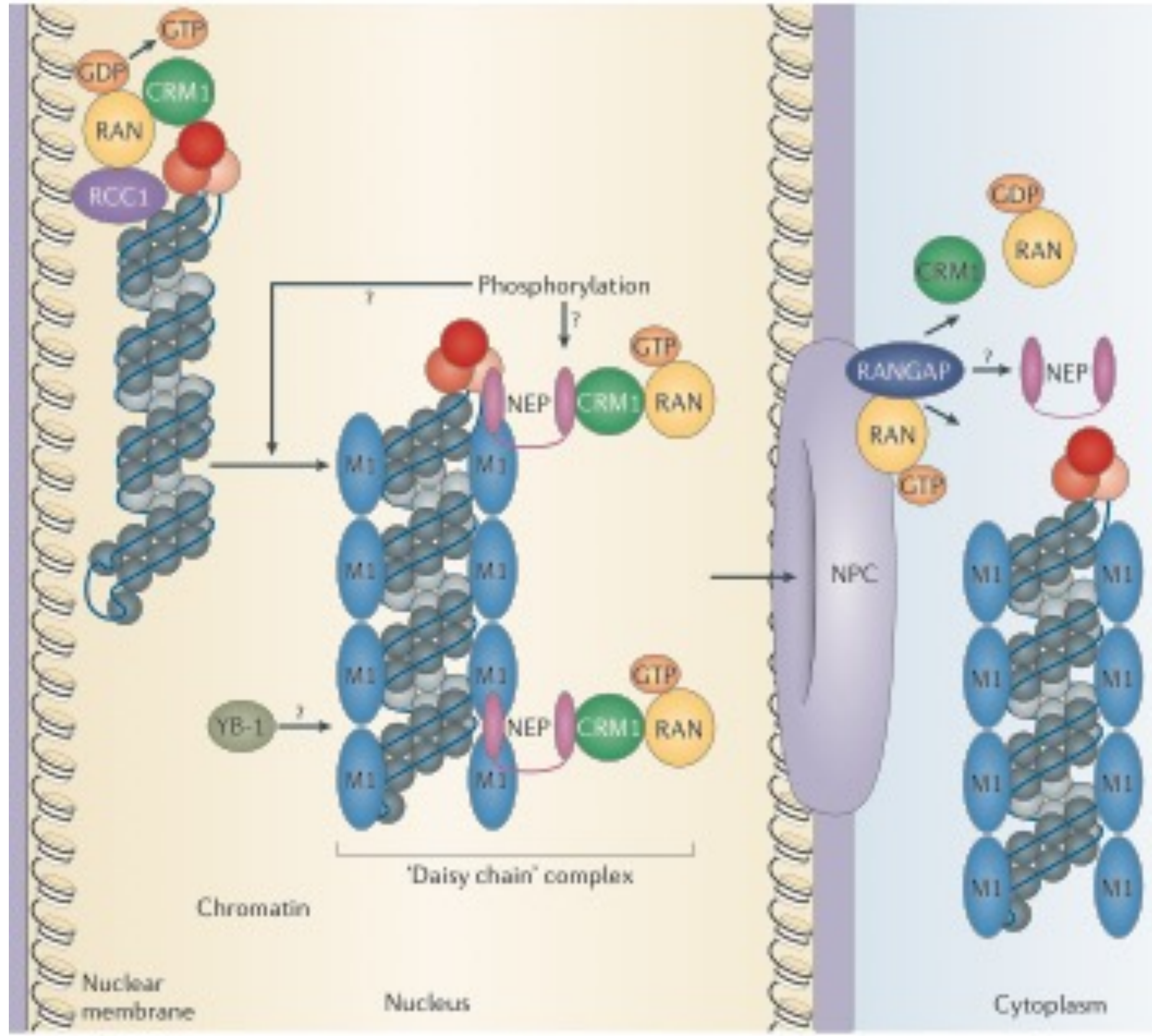
<u>The “daisy chain” model</u>

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

Crm1 is an importin $\beta$
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 – inefficent splicing
as a built in “molecular timer” (Chua, 2013)

Eisfeld 2014

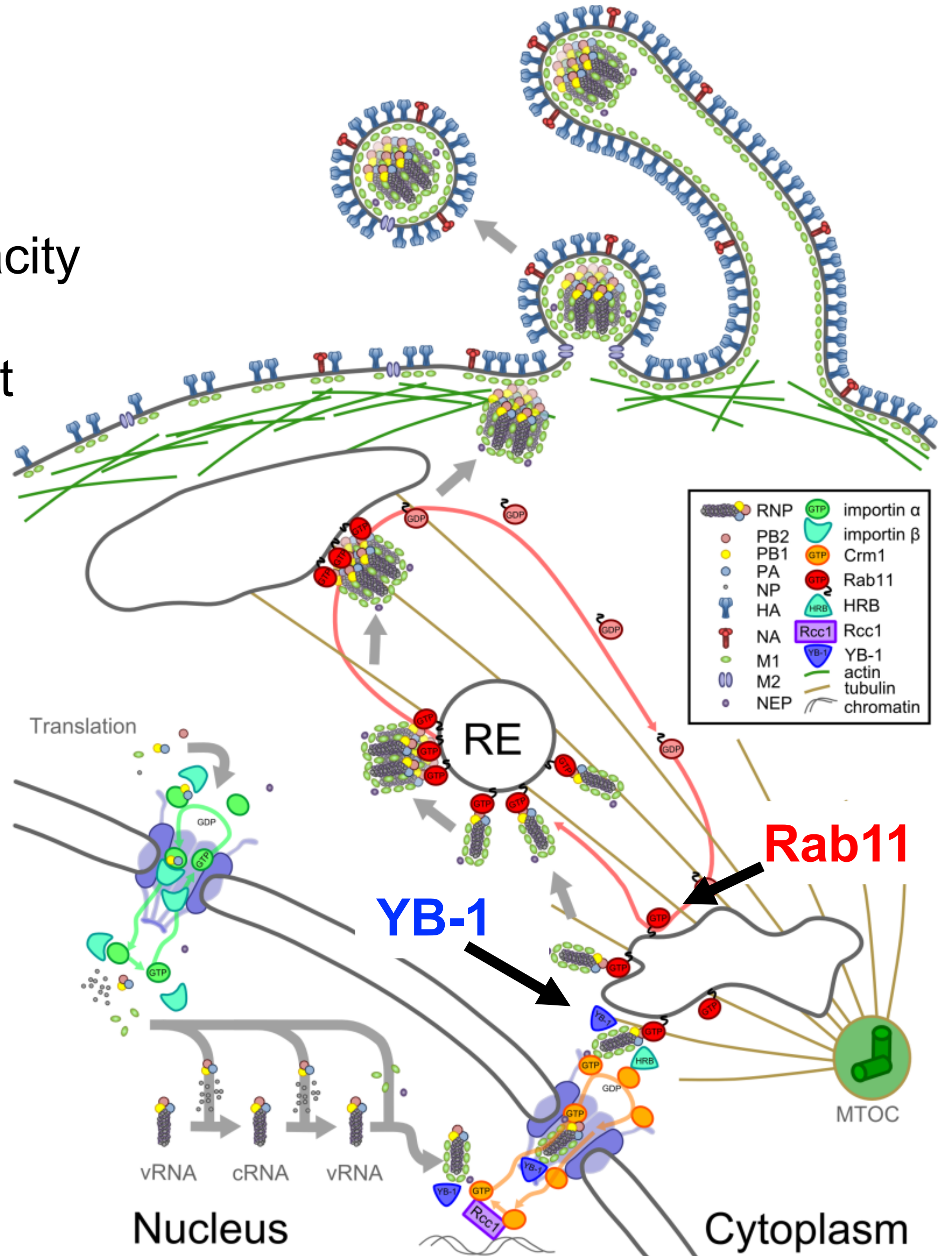
# vRNP trafficking

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




Hutchinson & Fodor 2013 Viruses

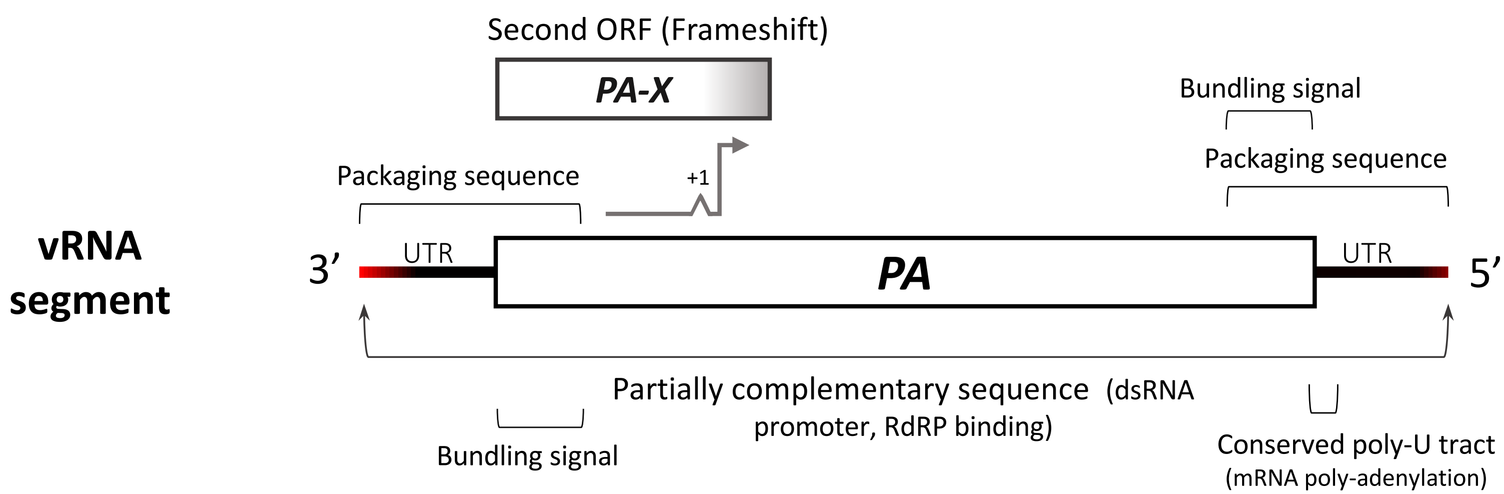
# How can you study polymerase, NP or RNP movement in real time during infection? A reporter virus.

**Benefits:**

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

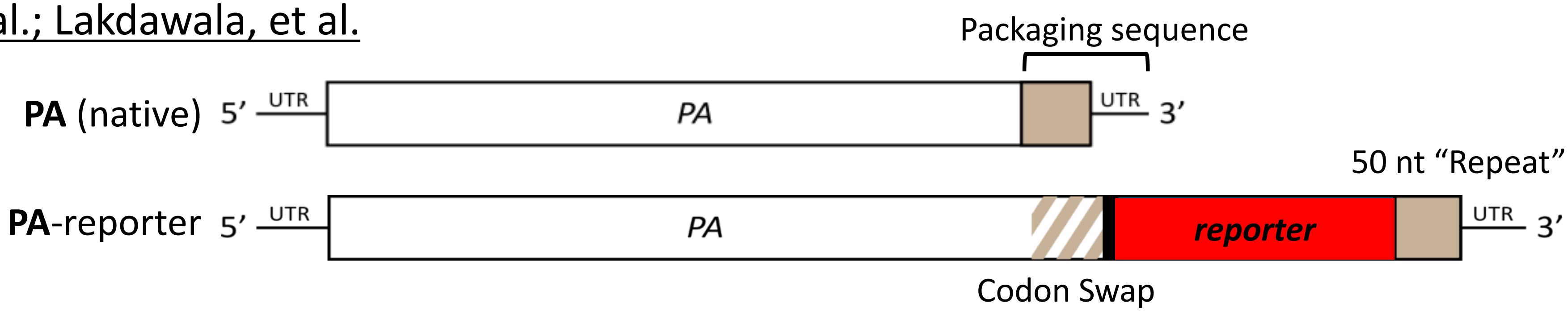
**Challenges:**

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



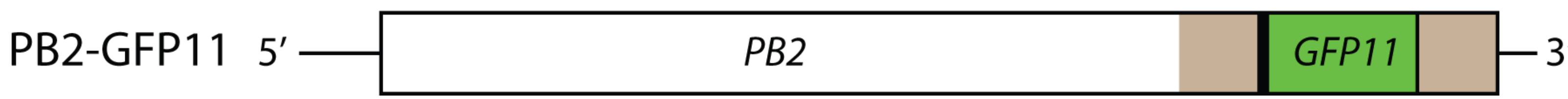
# Influenza reporter viruses

<u>Tran, et al.; Lakdawala, et al.</u>



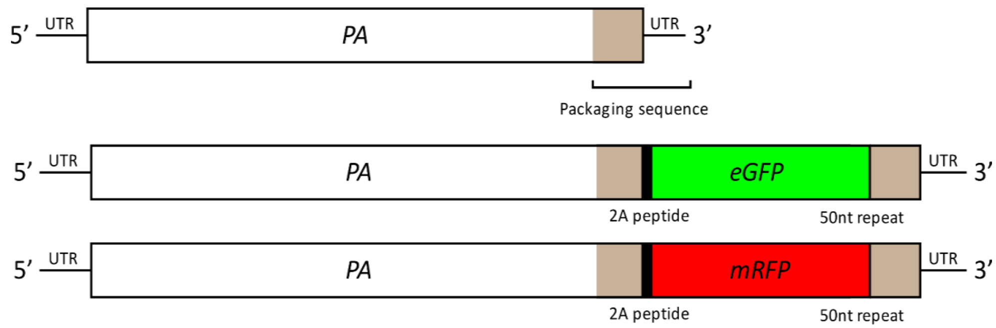

- Fusion to C-term of polymerase subunit
- Restoration of packaging signals by repeating 50 nt of PA ORF
- Codon swap increases stability

<u>Avilov, et al. – PB2</u>

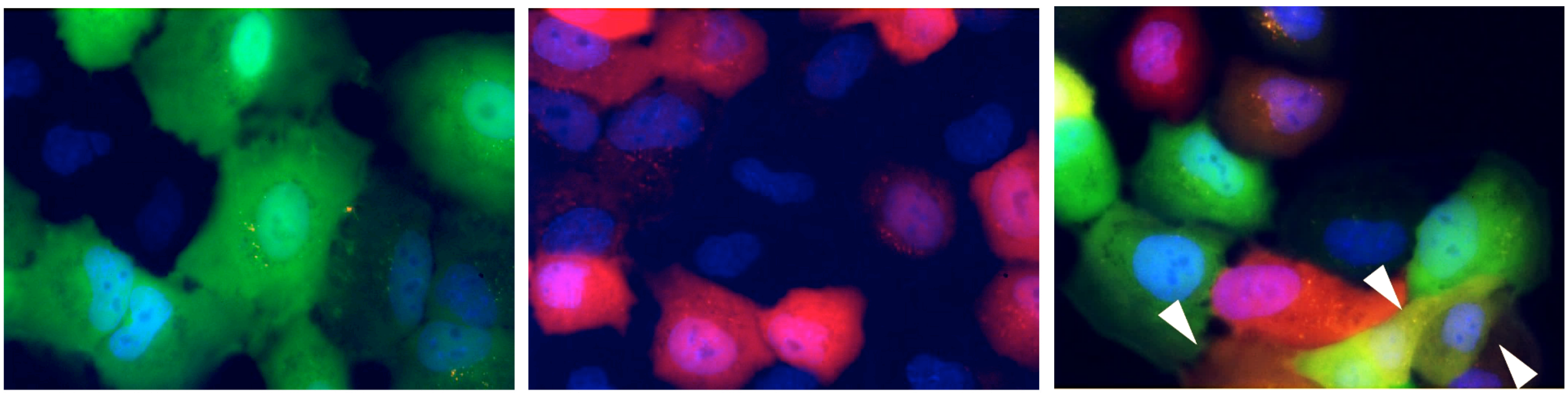



- Fusion to very small GFP11 to C-term of polymerase subunit
- GFP11 is a single beta sheet taken from GFP. Not fluorescent on its own
- PB2-GFP11 reconstitutes GFP in cells expressing GFP 1-10

# Detecting co-infection with PA-fusion viruses

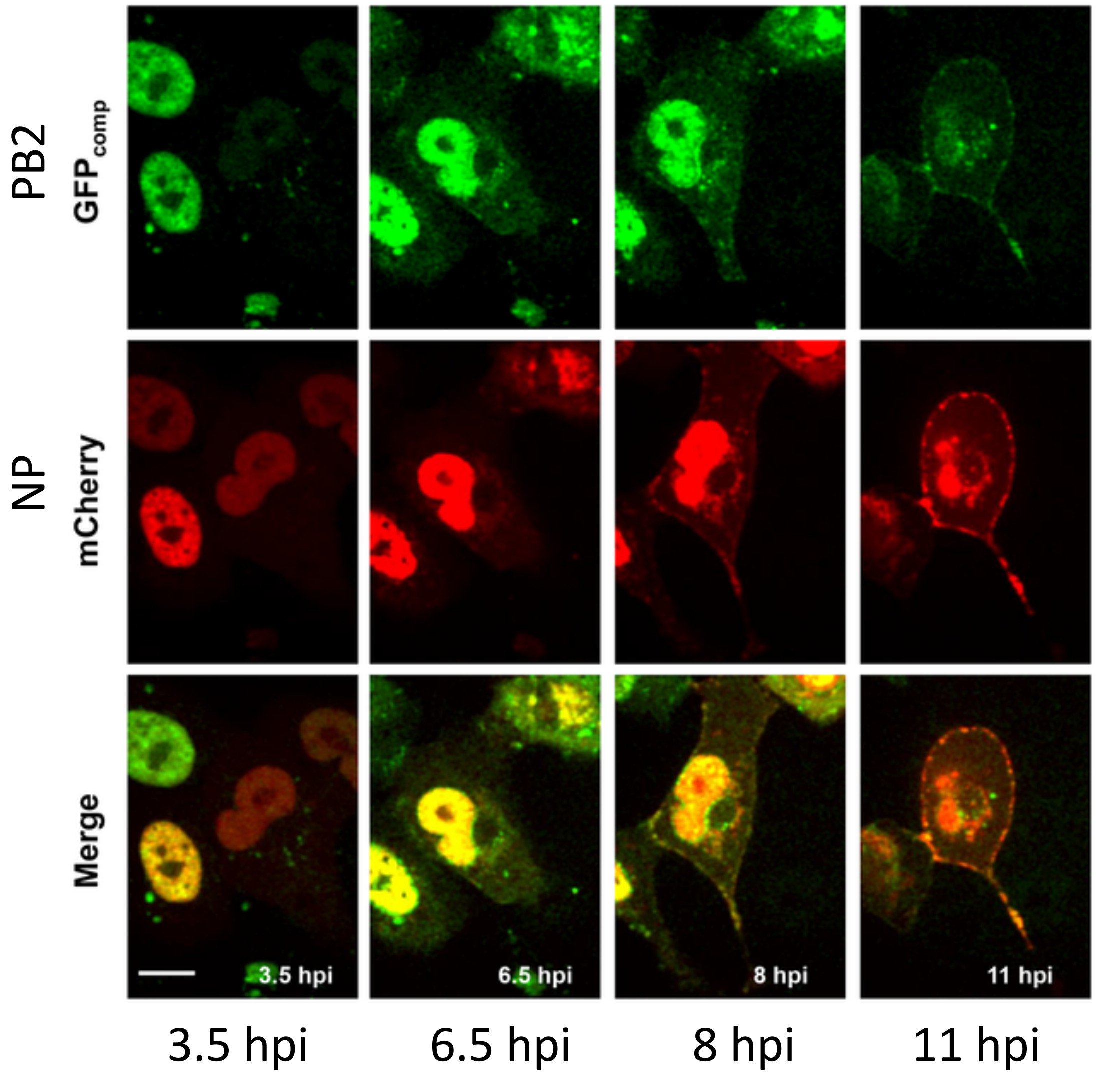



Virus: GFP RFP GFP+RFP



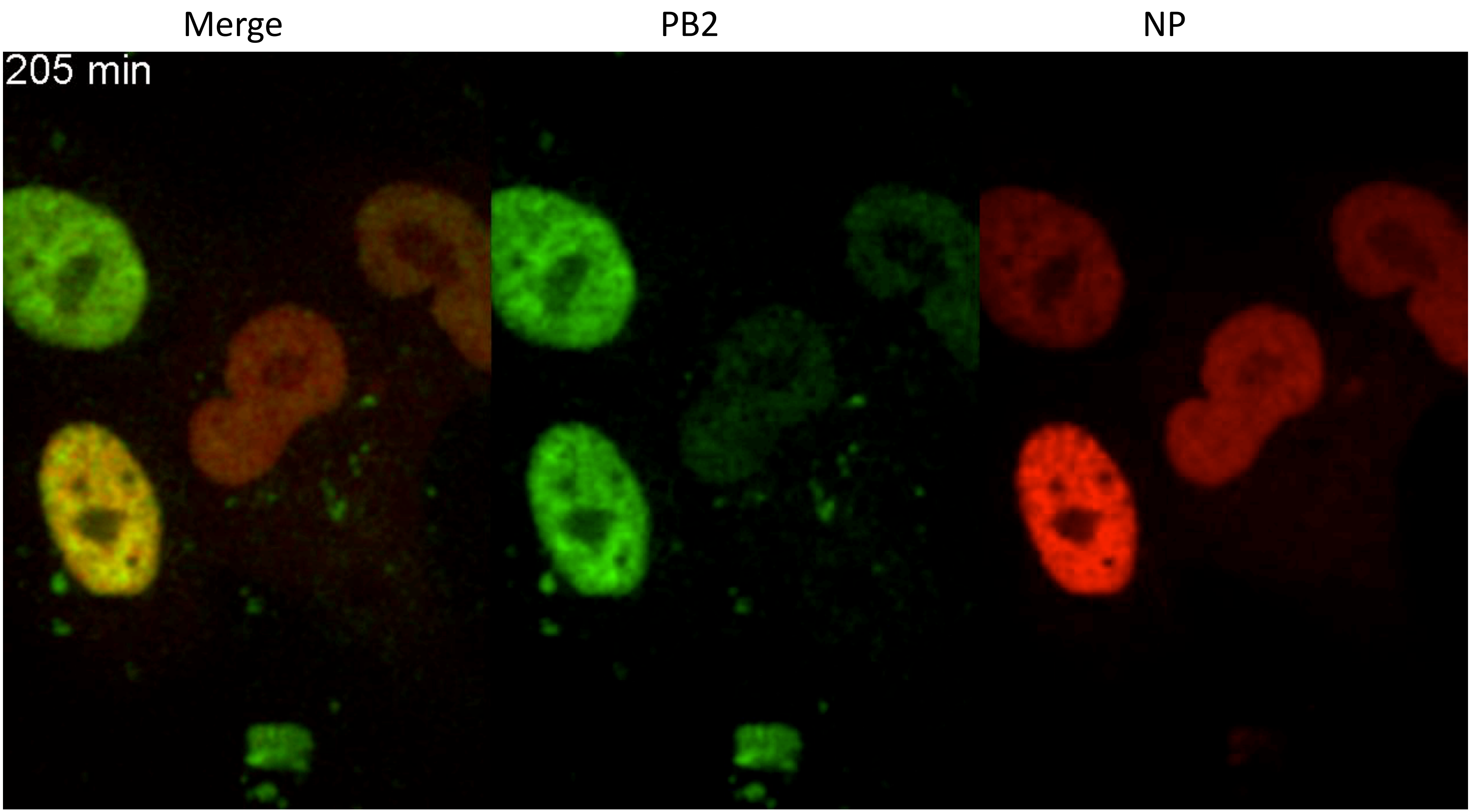
Tran *et al*. (2015)

# Tracking RNP export with PB2-GFP11 and NP-mCherry




Avilov et al. 2016 https://doi.org/10.1371/journal.pone.0149986

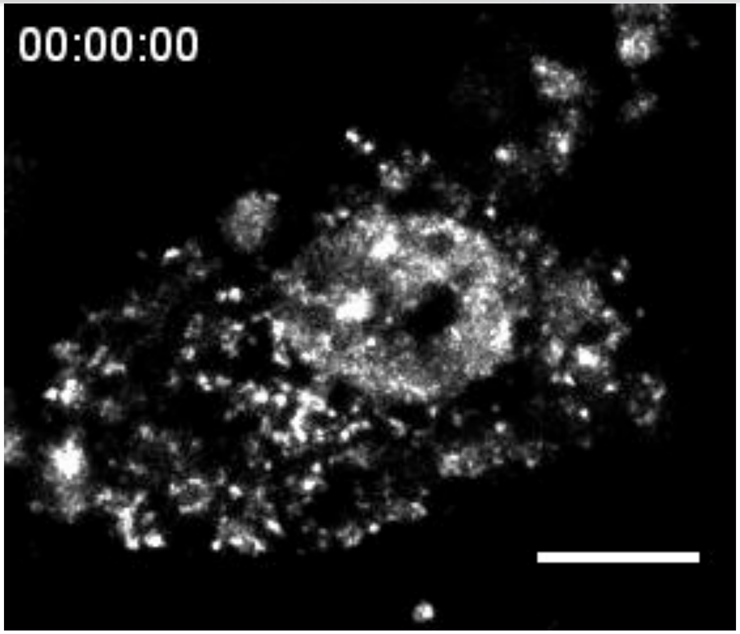
# Tracking RNP export with PB2-GFP11 and NP-RFP




Vero cells

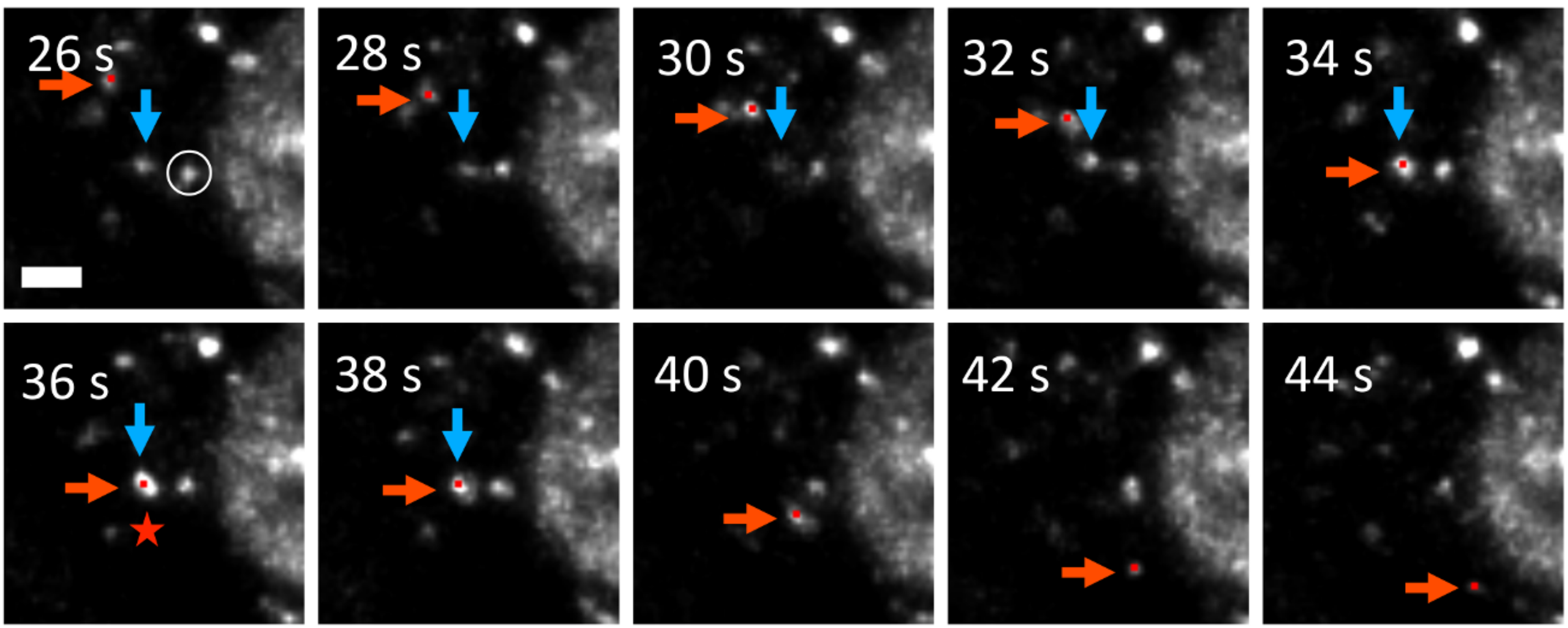
Avilov et al. 2016 https://doi.org/10.1371/journal.pone.0149986

# Tracking export with PA-GFP suggests RNPs bundle in cytoplasm



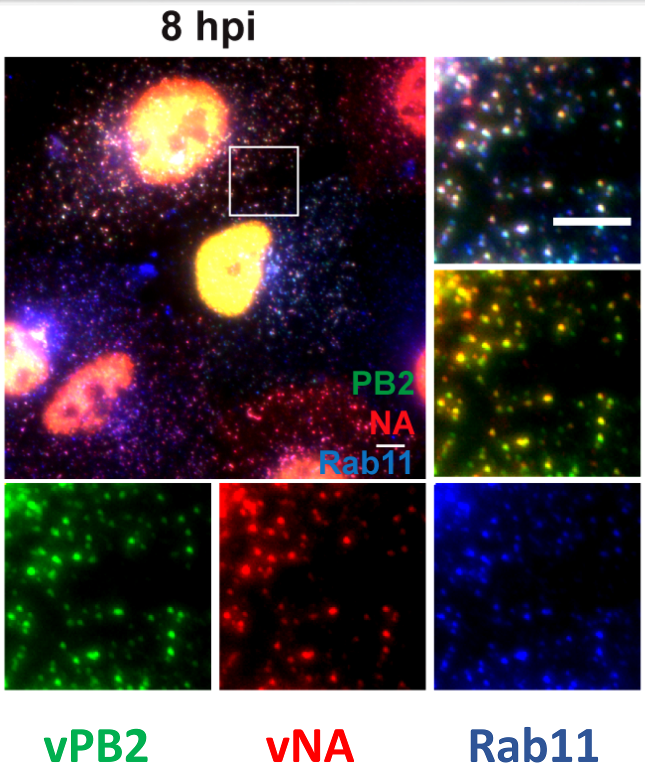

MDCK cells

distinct vRNPs assemble in cytoplasm




Lakdawala, et al. PLoS Path 2014

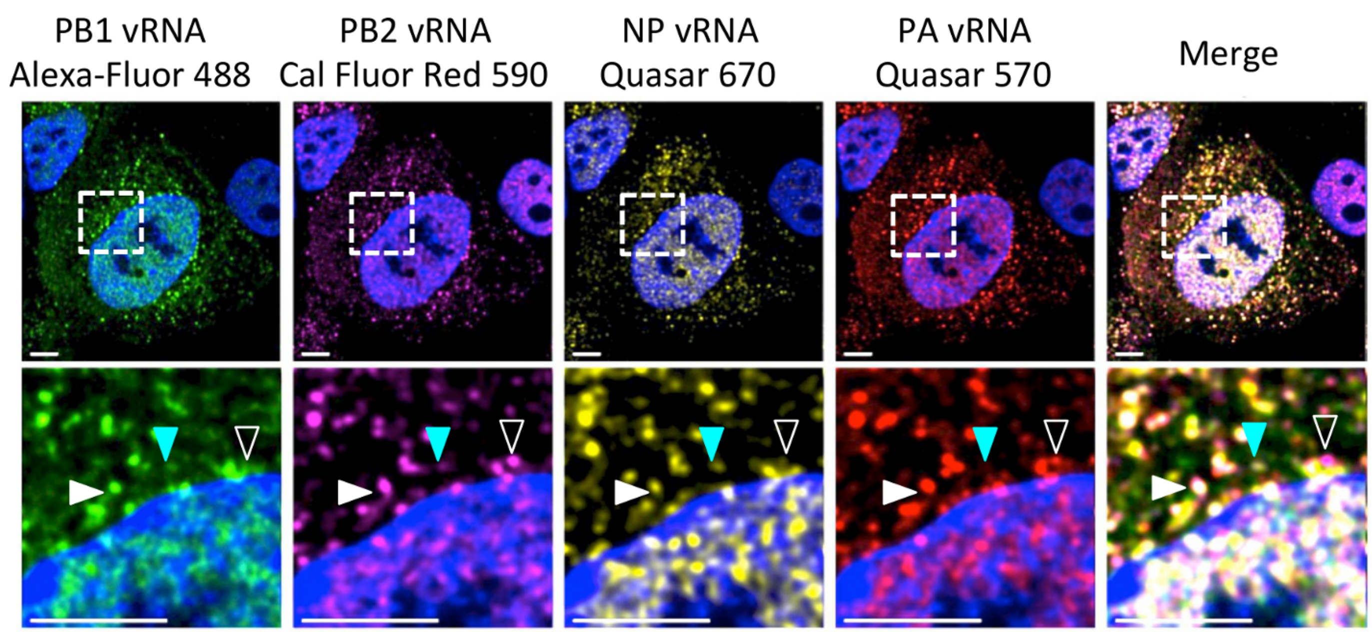
# vRNPs form "super assemblies" of different genome segments on Rab11 vesicles in cytoplasm




Unknowns:

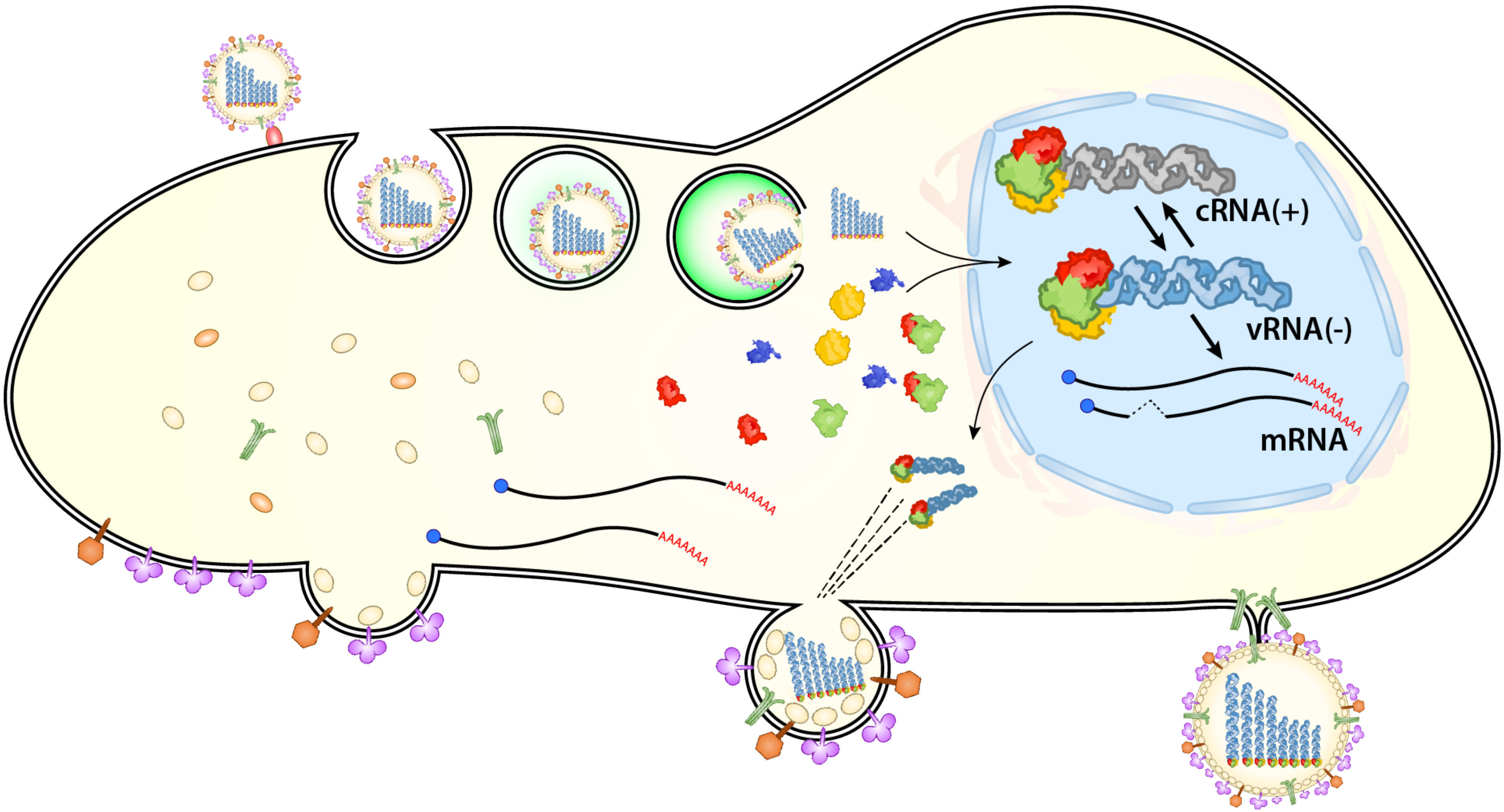
- how and where do vRNPs interact? bundling signals?
- how do virions get 8 distinct vRNPS?
- where does reassortment occur?
- when can reassortment occur? As long as infections occur within ~3hr of each other (Dou 2017 Cell Reports)
- how do RNPs go from RE to plasma membrane?
- do RNPs initiate budding?

co-localization of export RNPs



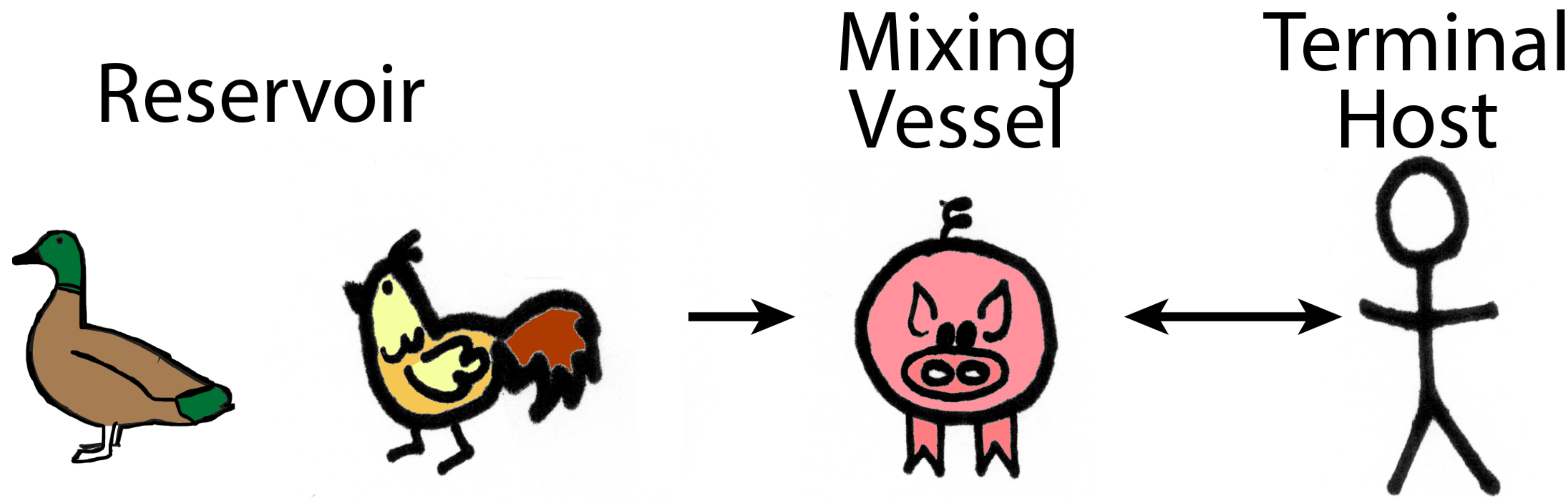

Chou 2013, Lakdawala, 2014

# The influenza virus replication cycle

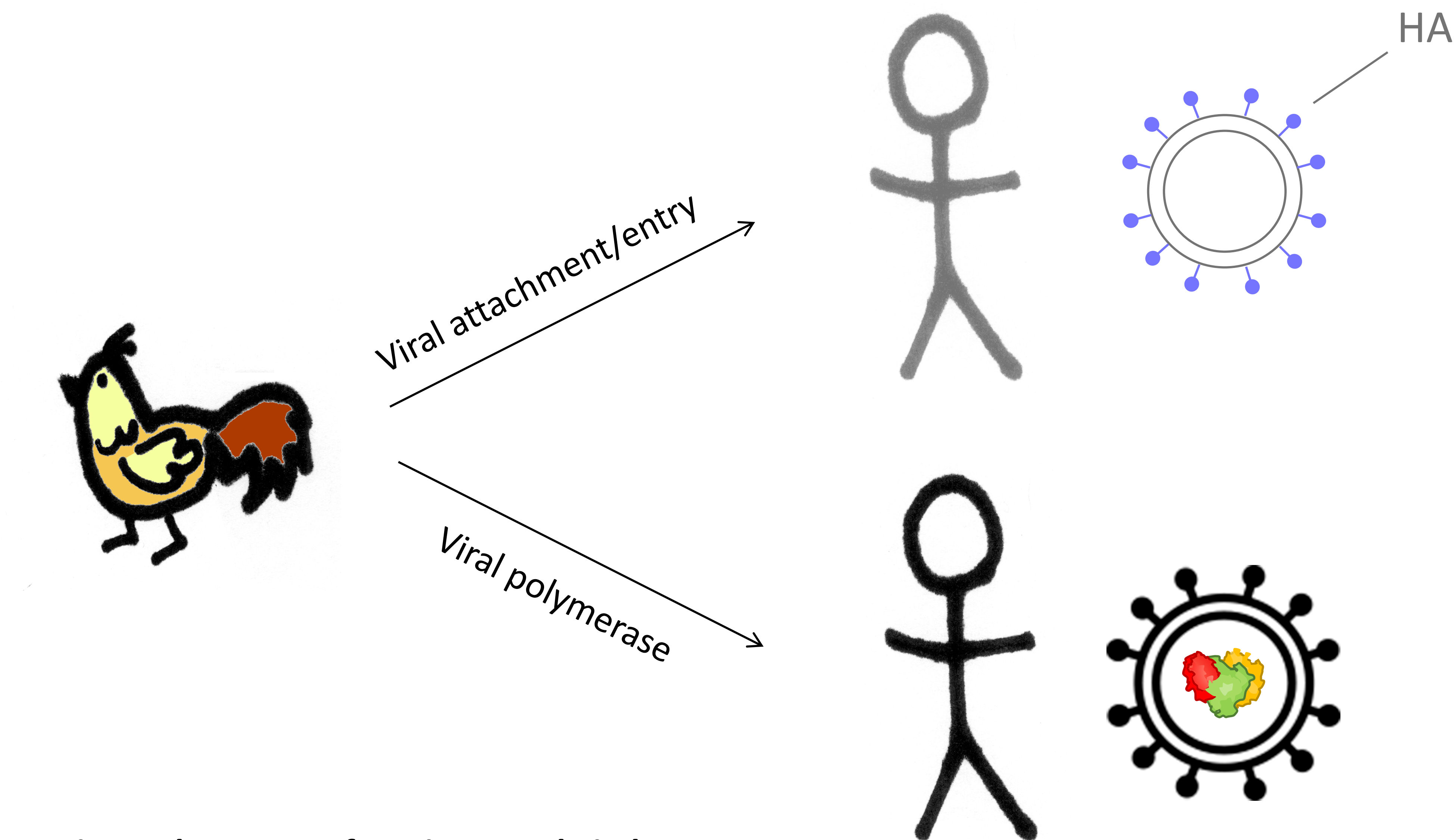


## Can cellular co-factors control influenza virus species tropism?

# Cross-species transmission of influenza

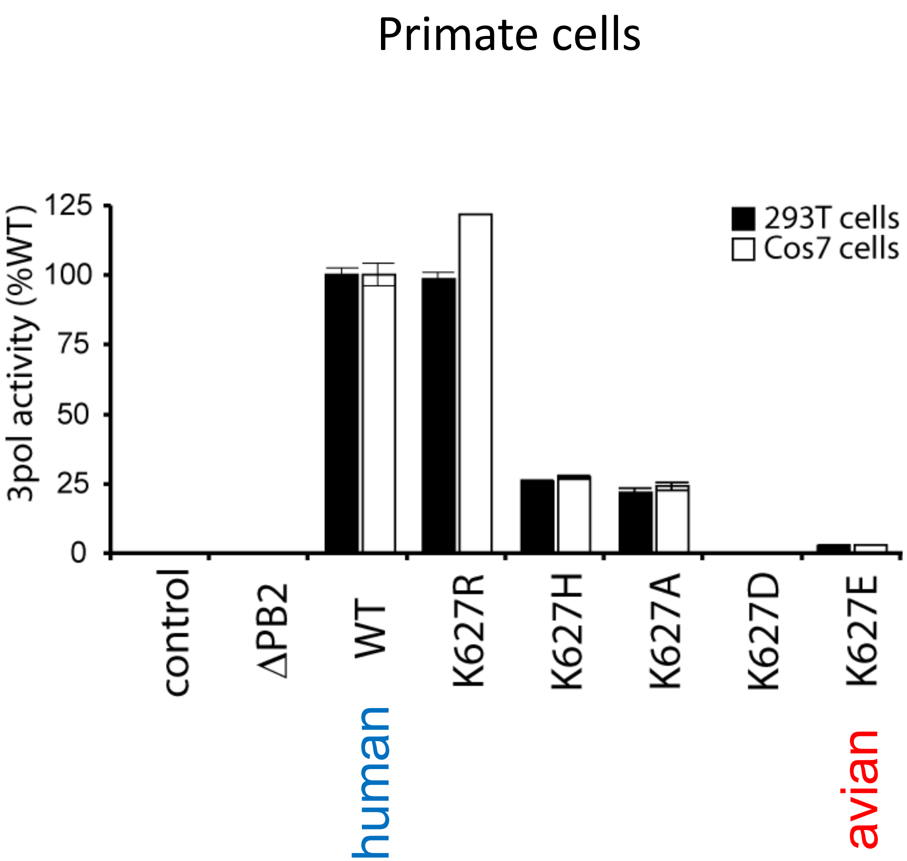


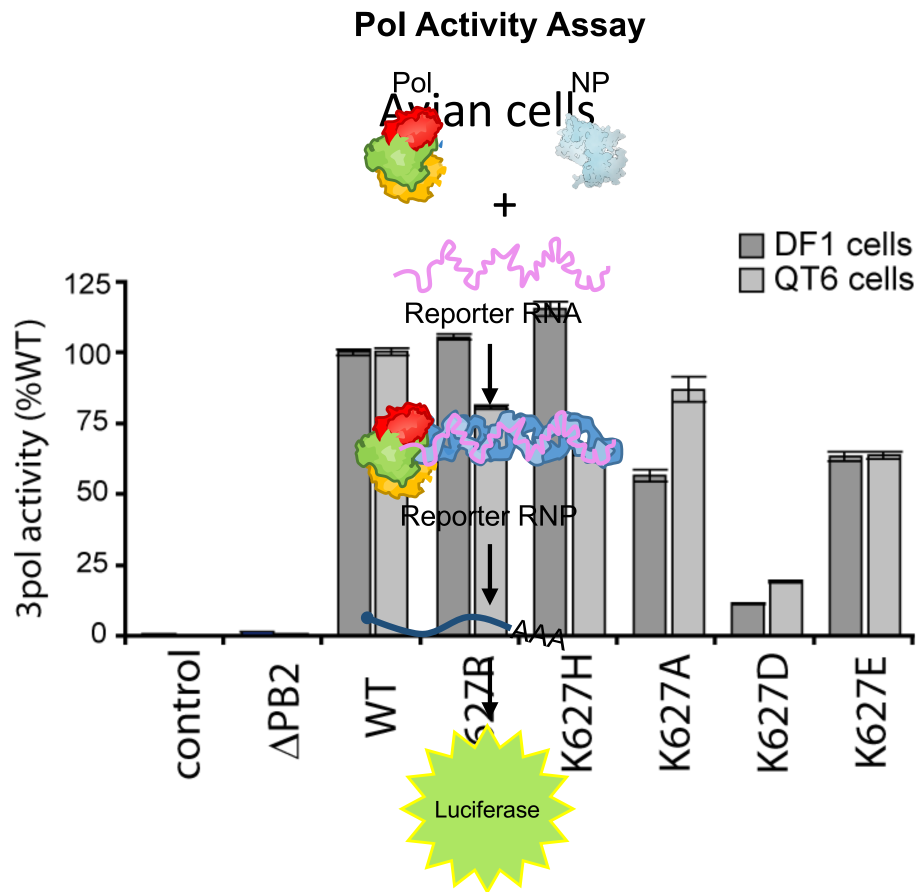
# Two predominant blocks to cross-species transmission




***avian polymerases function poorly in humans***

# PB2 aa627 regulates polymerase activity in human cells

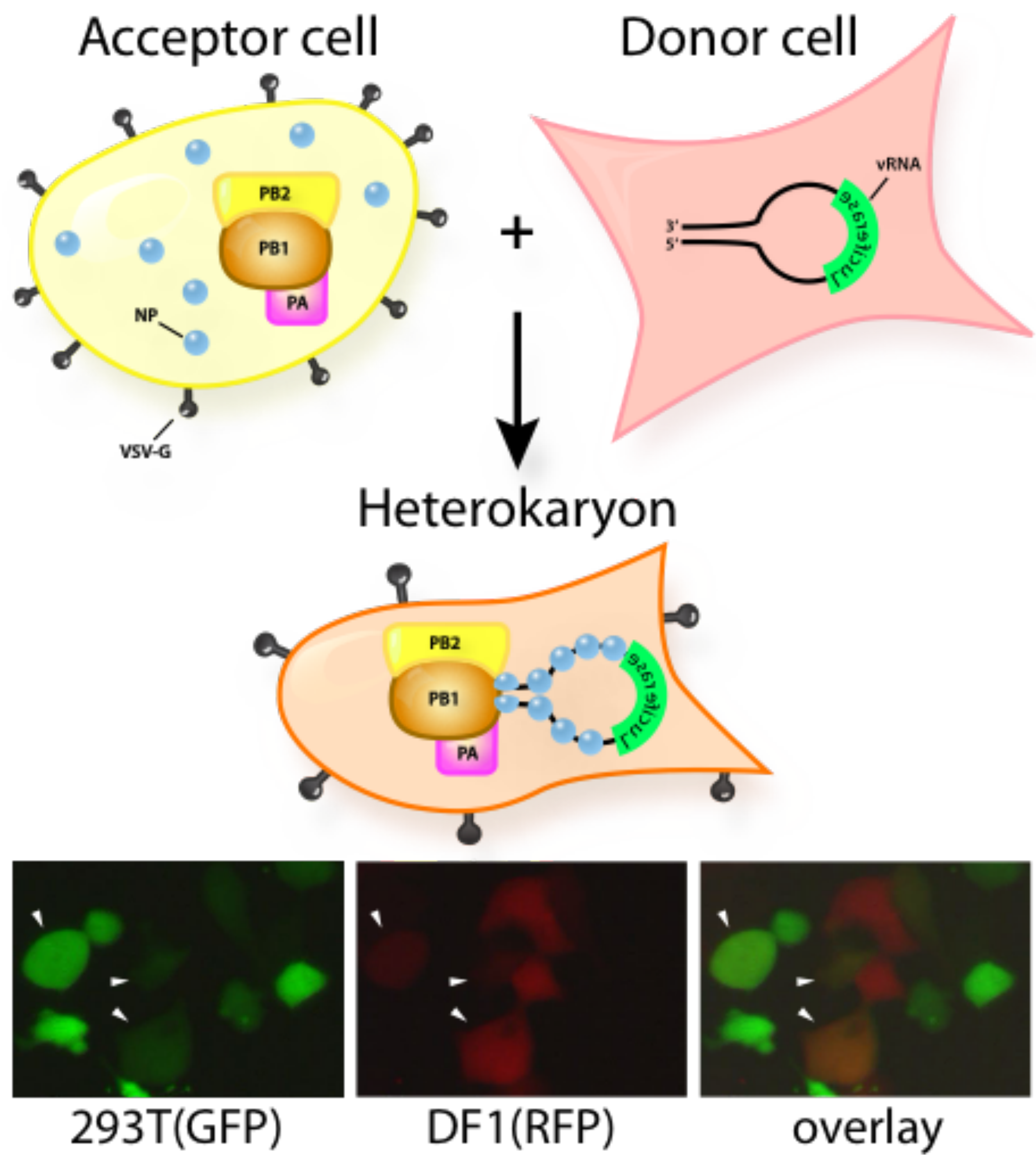


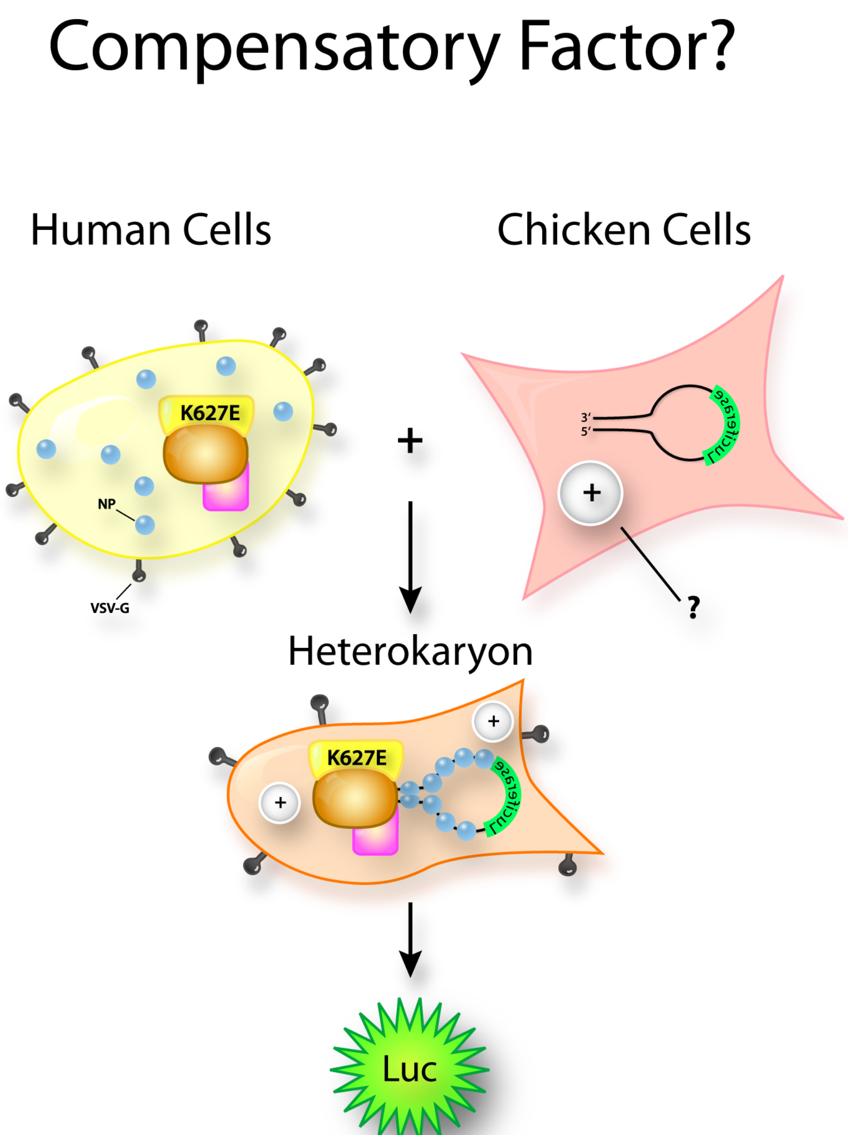

Subbarao 1993
Mehle 2008
Labadie 2007

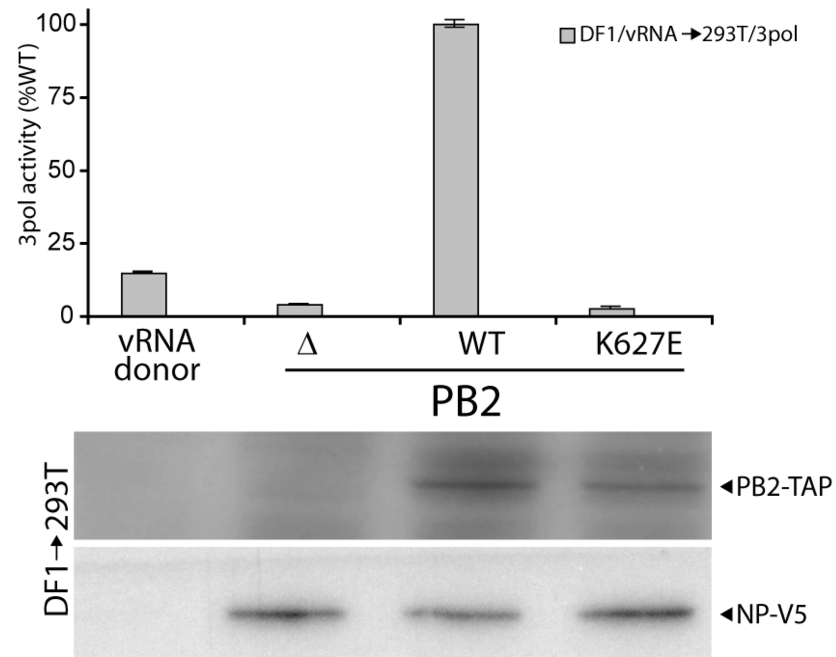
*restricted polymerases fail to assembly RNPs*

# Heterokaryon Assay



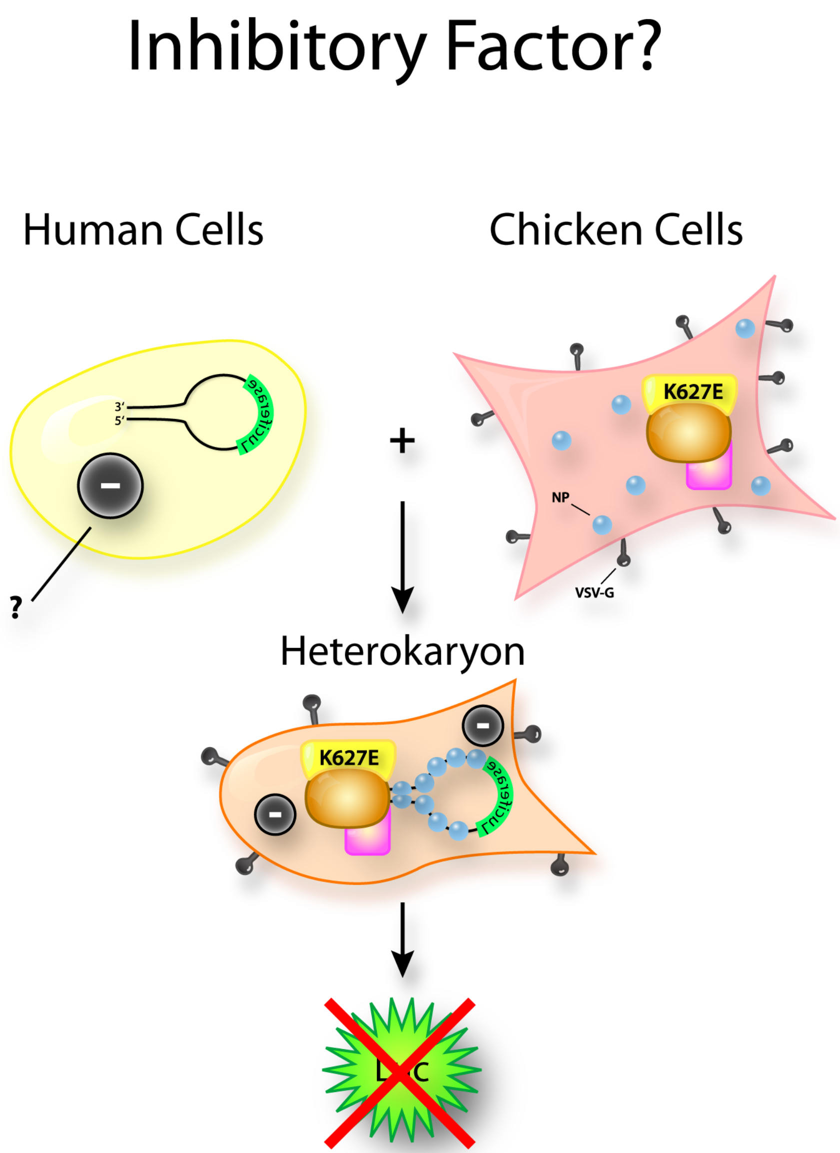
# Avian cells do not contain a compensatory factor

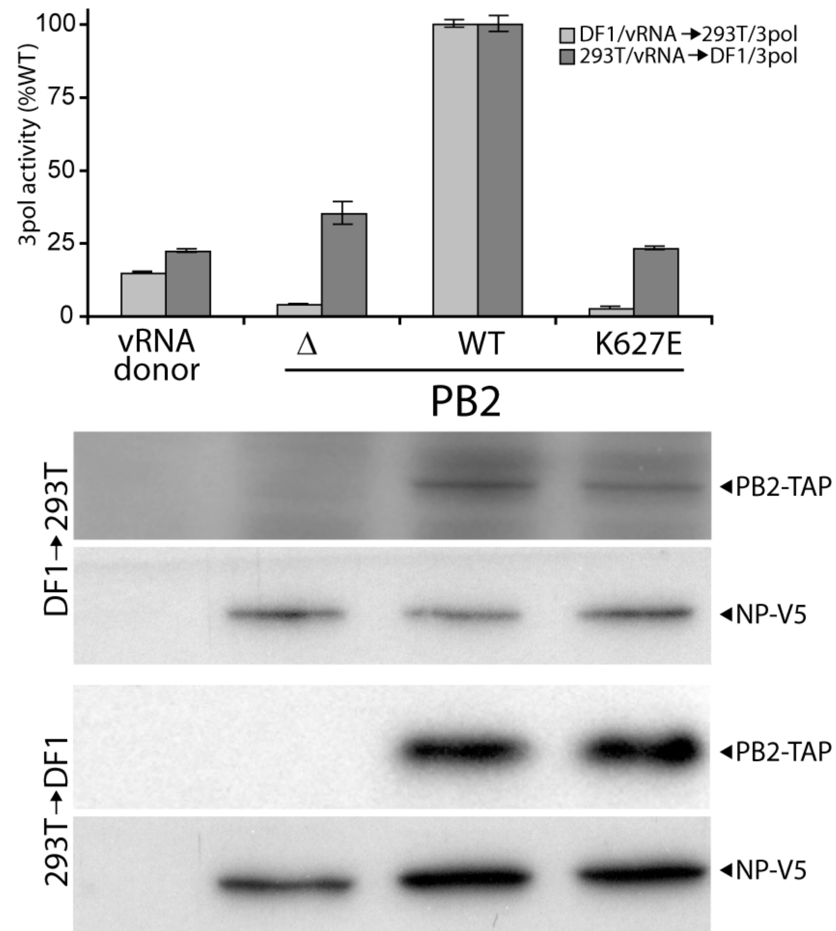


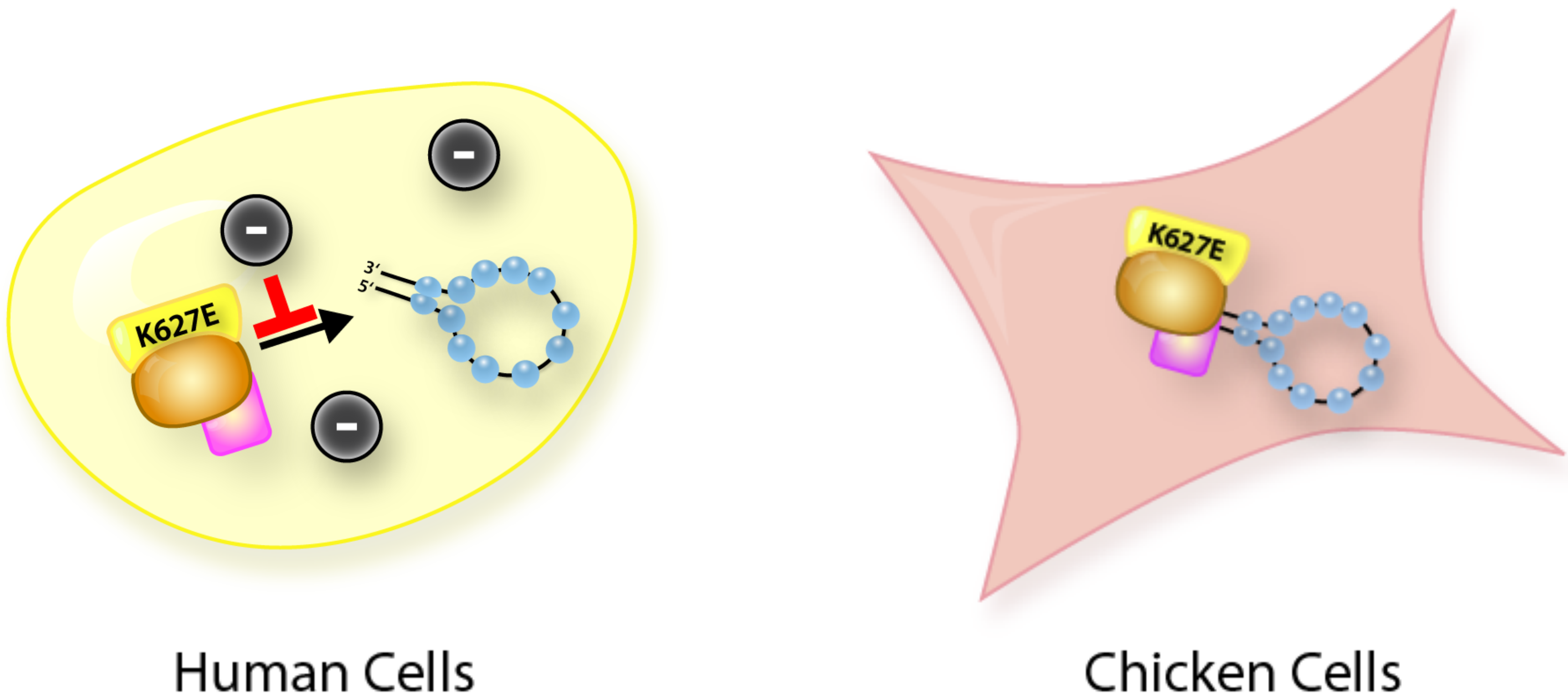

Mehle & Doudna 2008

# A dominant inhibitory activity restricts PB2 in human cells



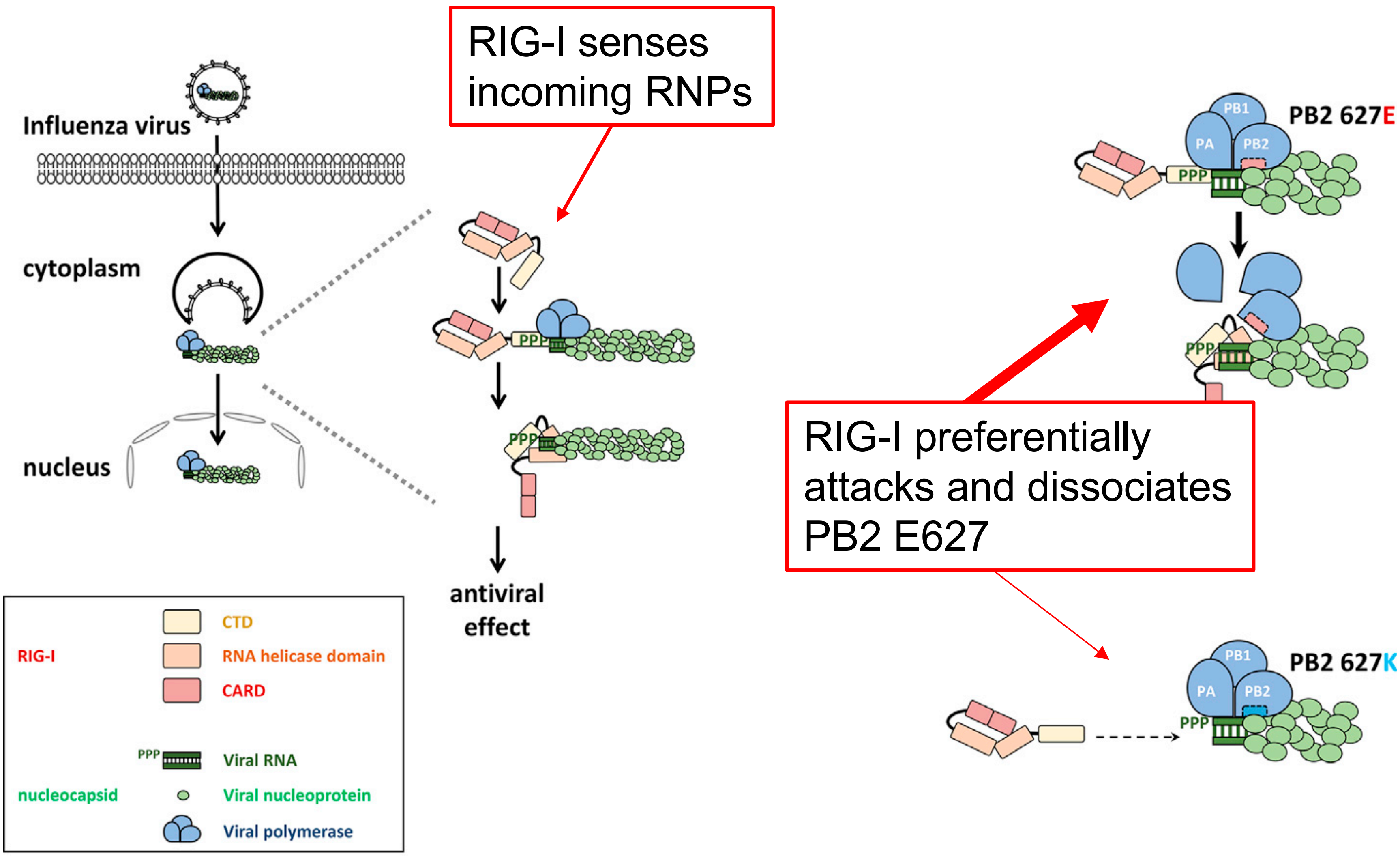



# A model for restriction of PB2 K627E



# Species-specific restriction of PB2 by RIG-I

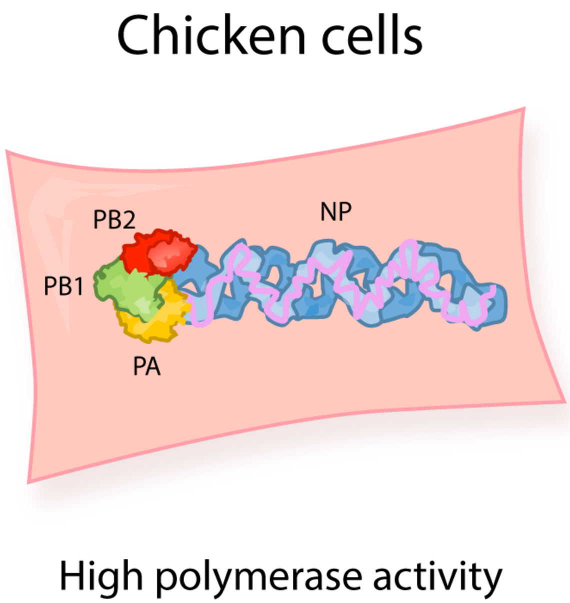
RIG-I – cytosolic sensor, recognizes 5’ ppp on RNA, initiates antiviral signaling
– absent from chickens

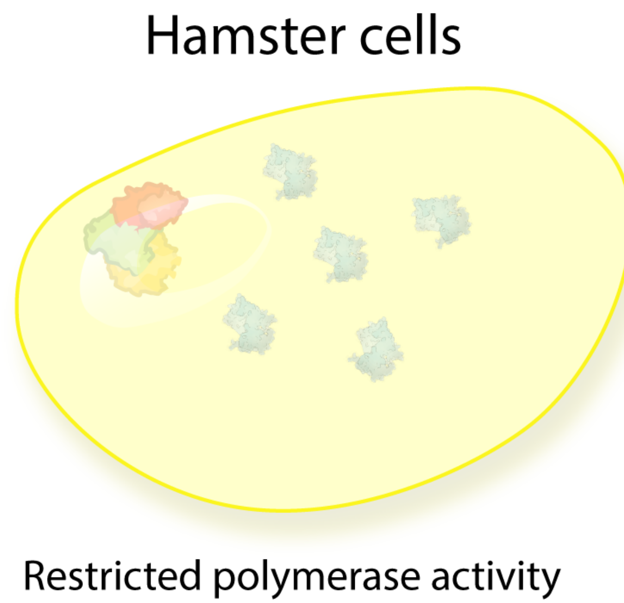



Weber, et al. 2015 Cell H&M

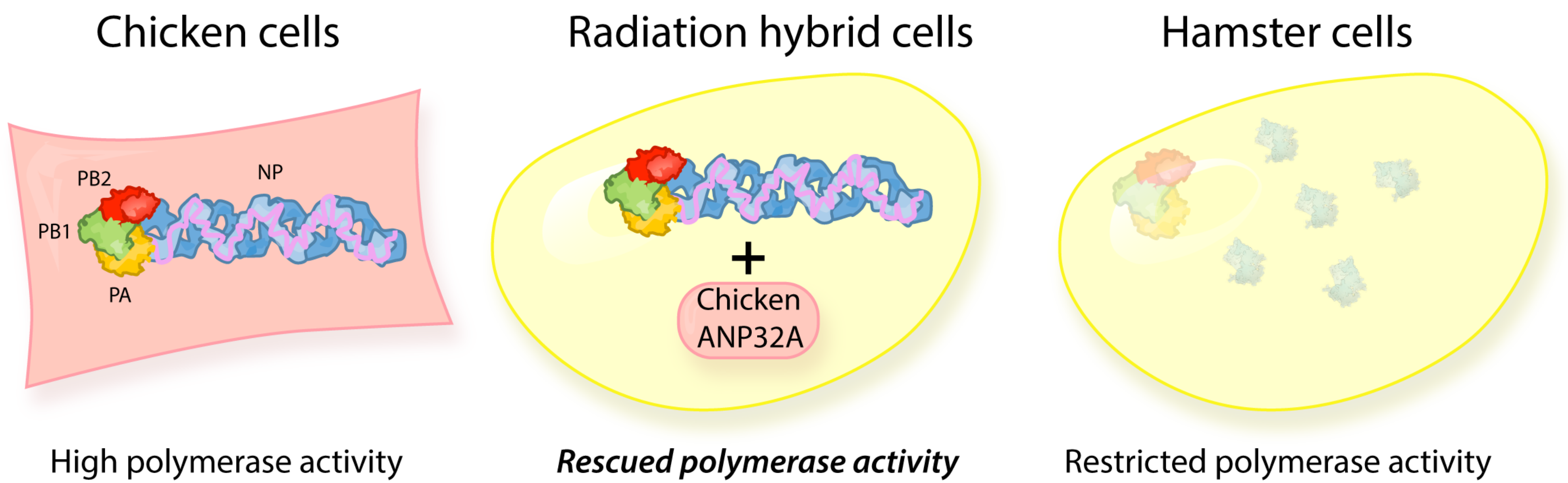
# ANP32A, a species-specific co-factor

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



# ANP32A, a species-specific co-factor

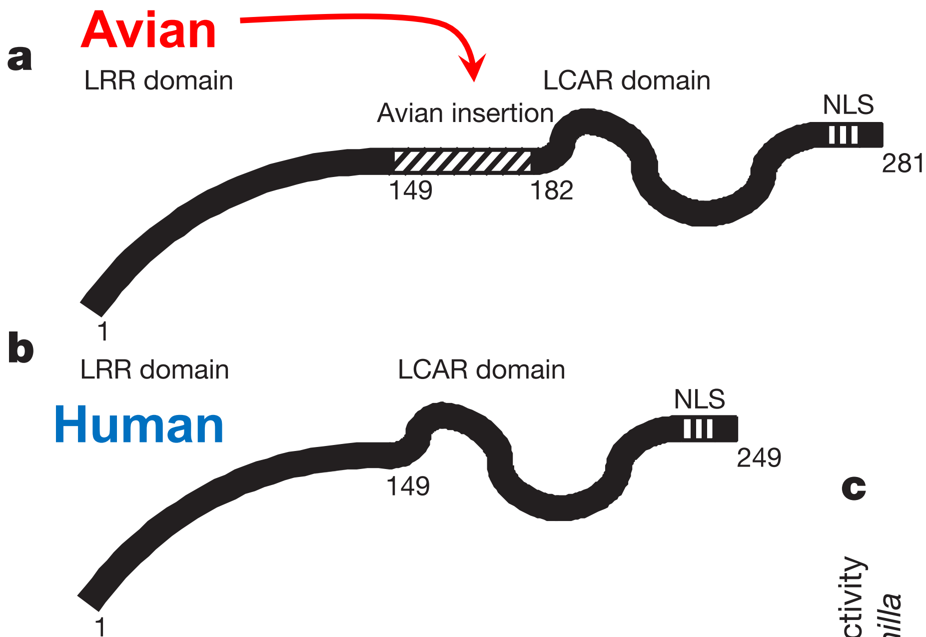



<u>ANP32A</u>

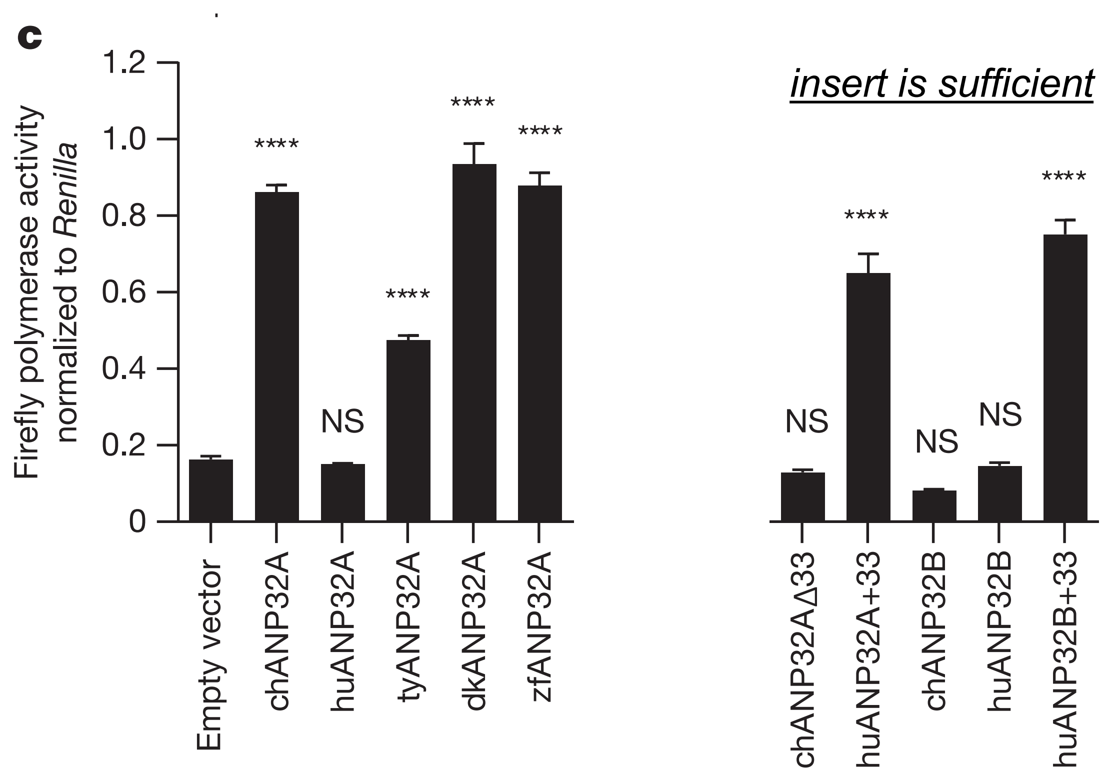
- N-terminal leucine-rich repeats, highly acidic low-complexity C-terminus,
- transcriptional control, cell death, mRNAtrafficking, and suppressing PP2A

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

# ANP32A, a species-specific co-factor



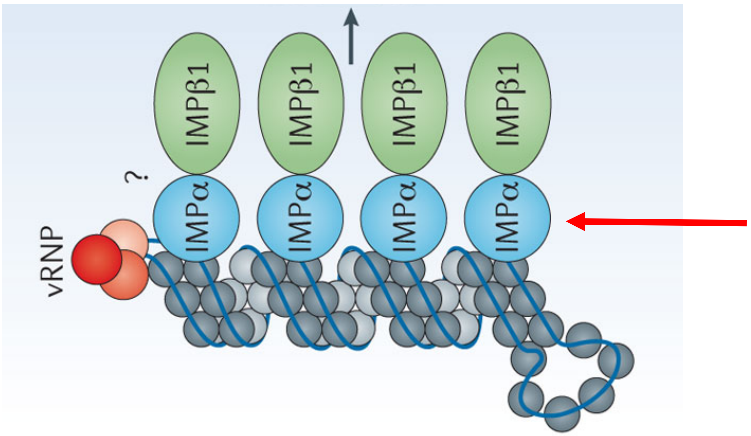

avian insert (exon duplication)
arises multiple times in birds




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

Long, et al. 2016 Nature

# Nuclear import as a species-specific regulator




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

Avian PB2 prefers IMPα3, human PB2 prefers IMPα7

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 IMPα'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, ACRC, ACSL1, ACSL4, ACTC1, ACTL6B, ACTN2, ACVR1C, ACVR2A, ADAM8, ADAMTS1, ADAMTS2, ADAMTSL4, ADAT1, ADCY7, ADRA1B, ADRB2, ADRBK2, AFF2, AGTRAP, AHCY, AHCYL1, AHNAK2, AHR, AIG1, AKAP11, AKAP13, AKT1, AKT3, ALAS1, ALG10, ALG6, ALPK2, AMHR2, AMMECR1, AMN, AMOTL1, AMOTL2, ANAPC2, ANGPTL3, ANKK1, ANKMY2, ANKRD7, ANKS6, ANPEP, AP2B1, AP2M1, APBA3, APBB1IP, APC, APC2, APOA1, APOA5, APOBEC3G, APOL6, APP, APPBP1, AQP4, AQR, ARAF, ARCN1, ARD1, ARL4A, ARMCX5, ARNT, ARTN, ASAH1, ASPA, ATCAY, ATF1, ATF2, ATF4, ATG16L1, ATP13A1, ATP1A2, ATP1A3, ATP2C1, ATP5B, ATP5C1, ATP5F1, ATP5I, ATP6AP1, ATP6AP2, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V0E2, ATP6V1A, ATP6V1B2, ATP6V1G1, ATP8, AXIN1, B2M, B3GALT2, B3GNT7, B4GALT2, BACE1, BACH2, BAIAP2, BAIAP3, BANP, BARHL2, BCAS2, BCL10, BCL3, BCR, BHLHB2, BID, BIRC1, BIRC8, BLNK, BMPR1A, BMPR1B, BMPR2, BRPF1, BRWD3, BST2, BTG1, BUB1B, BUB3, BZRAP1, C10orf57, C11orf60, C11orf82, C12orf47, C12orf5, 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NFAT5, NFE2L1, NFIL3, NFKB1, NFKBIA, NFKBIE, NFKBIL2, NFXL1, NFYA, NHP2L1, NINJ1, NKIRAS2, NKX3 1, NLGN4X, NLRC4, NLRP10, NLRP14, NLRP9, NOD1, NOD2, NOS3, NOSTRIN, NPAS1, NPY1R, NR2F1, NR4A1, NR4A2, NRBP1, NRP1, NT5C, NT5C2, NTHL1, NTRK1, NTRK2, NTSR1, NUDCD3, NUDT4, NUP107, NUP153, NUP205, NUP214, NUP43_HUMAN, NUP88, NUP98, NUPL1, NUTF2, NXF1, NXF3, NXT2, NYD SP25, OAS1, OASL, OLFM1, ONECUT2, OPN1SW, OPRS1, OR10H4, OR4M1, OR51T1, OSBPL6, OSMR, OSR2, OXSR1, P2RY12, P2RY2, PAGE5, PAICS, PAK2, PAK3, PALM2, PANK4, PAOX, PARP12, PART1, PASD1, PBK, PCCB, PCDH18, PCDHGA1, PCF11, PCGF6, PCK2, PCSK5, PCSK7, PCTK2, PCYOX1, PDCD10, PDGFA, PDGFRA, PDGFRL, PDK3, PDLIM3, PELI1, PEN2, PEPD, PEX11B, PEX14, PFTK1, PGD, PGF, PHF2, PHF20, PHF3, PHGDHL1, PHYHIP, PI4KA, PI4KB, PIGA, PIGH, PIGT, PIK3C2A, PIK3C2B, PIK3C2G, PIK3CB, PIK3CD, PIK3R2, PIK3R3, PIK3R4, PIK3R5, PIN1, PIP, PIP4K2B, PIP5K1C, PKD1, PLA2G10, PLA2G2F, PLA2G5, PLAU, PLCD1, PLCD3, PLCH2, PLD2, PLK2, PLK3, PLK4, PLP1, PLTP, PLXNA2, PLXNB2, 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PTGES3, PTPRE, RAB11A, RABGEF1, RACGAP1, RAN, RANGAP1, RBM15B, RBPMS, RHBDD2, RUVBL2, SAA2, SEMA3C, SENP2, SIAH1, SLC7A13, SNUPN, SPINK1, TACC1, TCF12, TFCP2, TOP3B, TRAF1, TRAF2, TRIP6, TRPT1, UBE2I, UGT3A1, USHBP1, VISA, XKR6, XPO7, ZNF131 **Y2H:**ACTB, C14orf166, CCHCR1, CHD6, CIAO1, CNRIP1, COPS5, CSRNP3, DCTN1, DRG1, EIF3S6IP, EIF4A2, FANCG, GOLGA2, GPR89A, IK, KAZR, KLC1, KLC4, LRRFIP1, LZTS2, MLH3, MNAT1, MYBL1, NBR1, NKX2 2, NMI, NNAT, NUP54, PARL, PCBD1, PCBP1, PITPNA, PLEKHG3, POLR2A, PPP1R12C, PRKRA, RANBP9, RC3H1, TAB2, TM7SF3, TNRC6A, TPR, USP22 **shRNA:**AB12, ABCB10, ACOT2, ACVR1B, ADAM11, APOBEC3G, ARRDC3, ATF1, ATG5, ATP6AP1, ATP6V0C, ATP6V1B2, ATP6VOD1, AXL, B3GAT1, BAD, BPTF, BRCA1, BTC, BUB1, C11ORF71, C13ORF28, C17ORF85, C1ORF56, C1QL3, C4BPA, C4ORD35, C6ORF136, C6ORF162, C6ORF57, CAMK1, CCNJL, CD200R1L, CDH26, CDKN1A, CEBPG, CENPH, CENPK, CFL1, CHMP2A, CLECL10A, CLOCK, CMTM1, COX5B, COX7B2, CRNN, DAPK2, DCLRE1C, DDX3Y, DLAT, DOCK5, DPPA2, DR1, DSG4, DYRK1A, EED, 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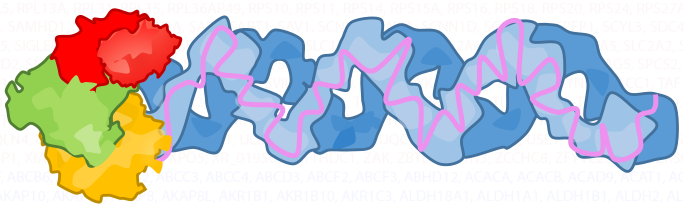
THOC6, TMC6, TMEM11, TMEM14A, TMTC4, TNFSF12 TNFSF13, TNFSF13, TNFSF9, TNRC6A, TPD52, TRIM13, TRIM16, TRIM16L, TRIM21, TRIM59, TTN, TXNDC16, UBXN7, UGT2B15, USP16, USP22, USP34, USP37, USP47, USP8, WNK2, WT1, XCR1, YPEL2, YWAH, YY2, ZCCHC14, ZCCHC4, ZFP2, ZNF251, ZNF397, ZNF71, ZSCAN12, ZSCAN16 **random_homozygous_insertion:**ADAM20, AKT1, ARID1B, CHM, COG5, COX5A, CSNK1D, DDX17, DDX58, GRK6, HEATR7A, HERC6, LRRC16A, LSM4, MDN1, MRPL42, N4BP2, NDUFA7, NDUFAF2, PKD2L2, RAD51L1, RHGP, SF3A3, SLC25A25, SLC30A9, STXBP1, VPS34, ZNF7 **haploid screen:** CMAS,SLC35A2

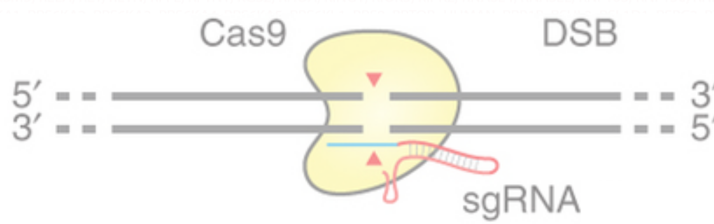
## Goal:

# Identify novel human host factors that regulate the influenza virus replication machinery

## Post-translation control of the RNP



## Exploiting antiviral responses




Arindam Mondal

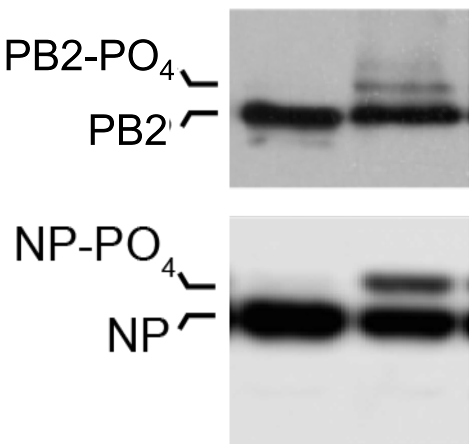
Tony Dawson

Vy Tran

Mitch Ledwith

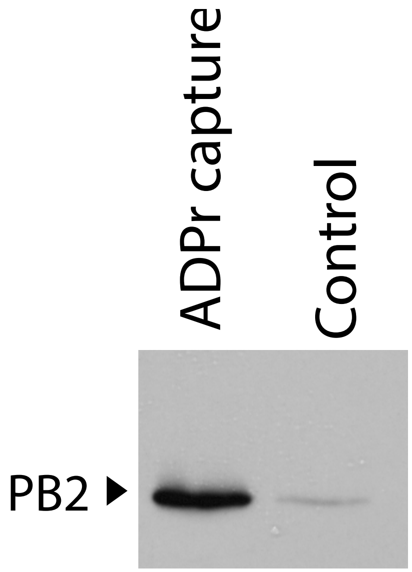
# Post-translation regulation of the viral replication machinery

**Phosphorylation**



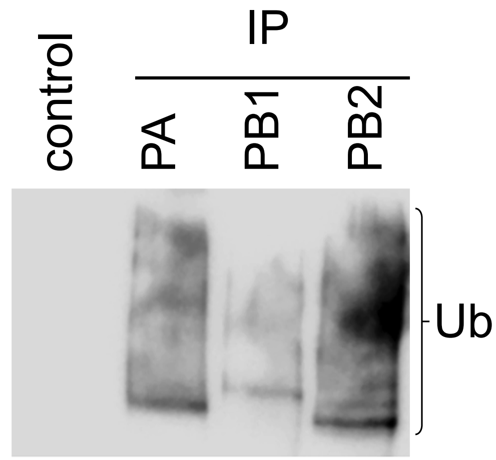

Mondal, 2015
Hutchinson 2012
Kistner 1985, 1989
Privalsky 1977

**ADP-ribosylation**




Liu 2015
Mehle unpub.

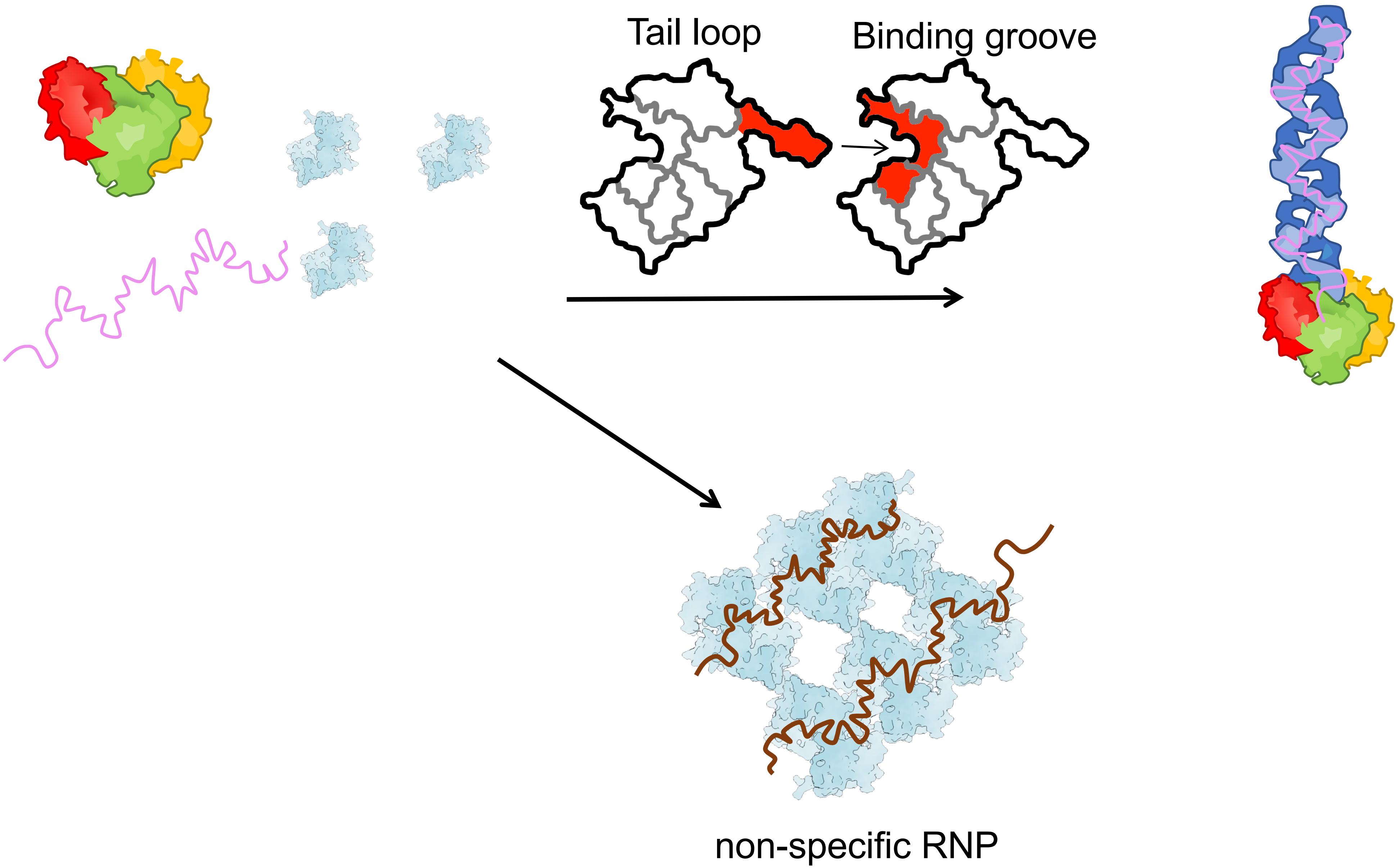
**Ubiquitination**



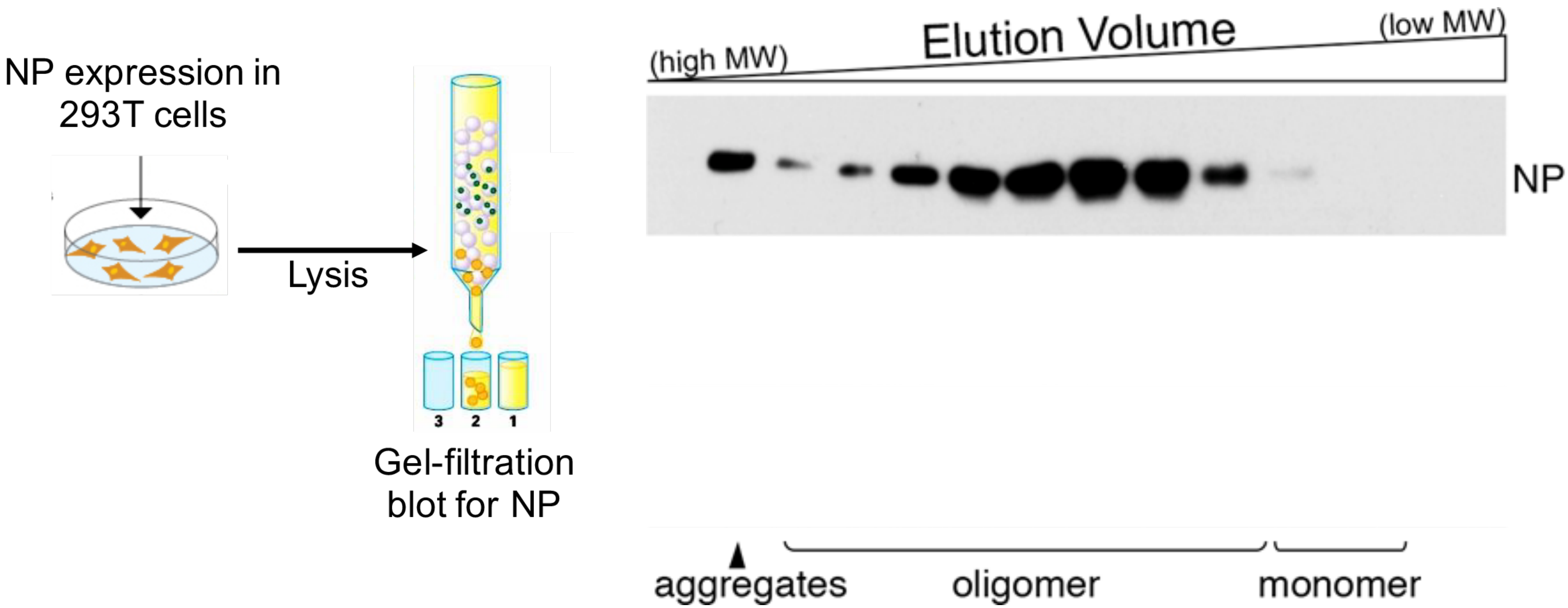

Kirui 2016
Liu 2015
Lin 2017
Liao 2010

**Others?**

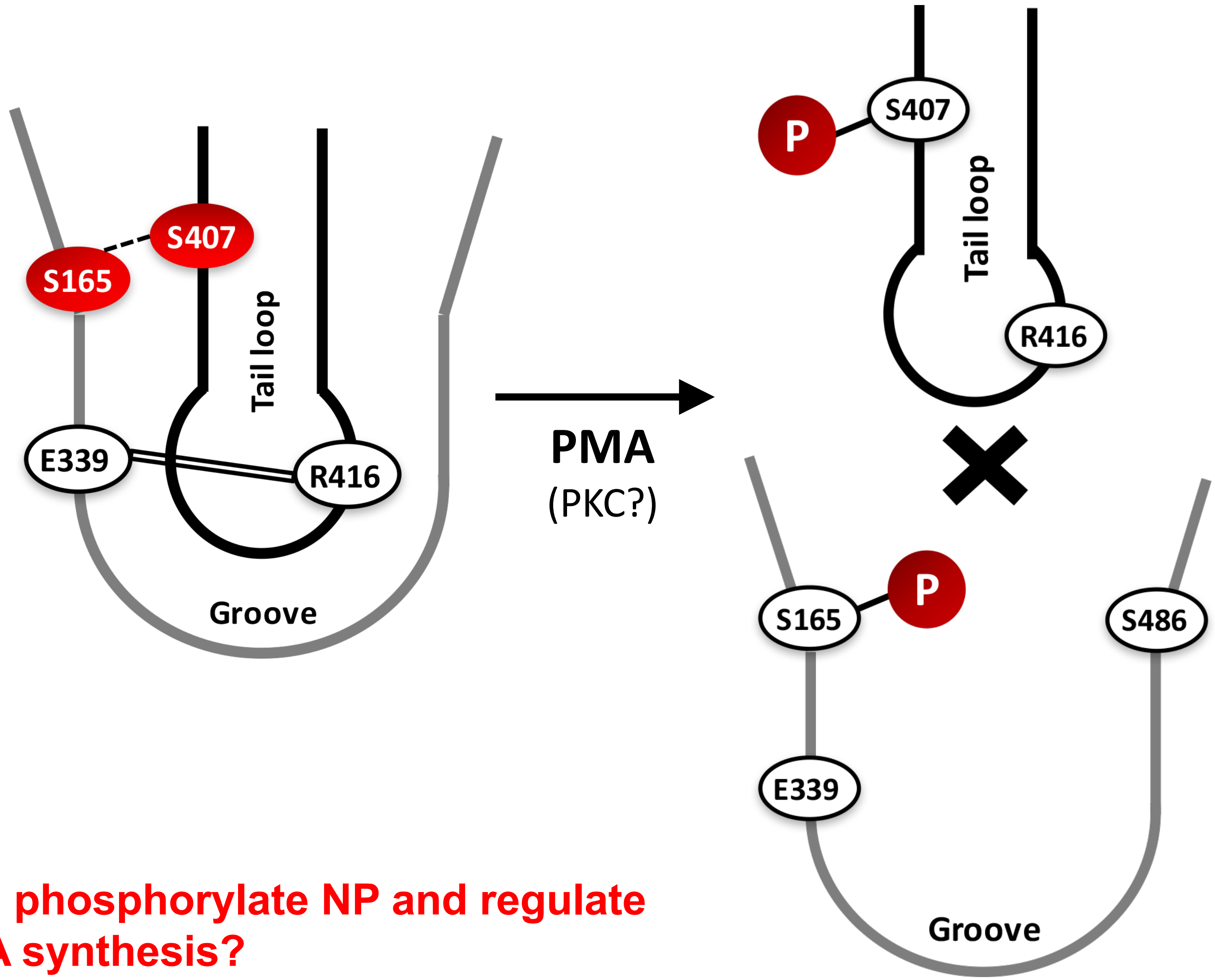
# The influenza RNP



# Phosphorylation of NP maintains a monomeric state



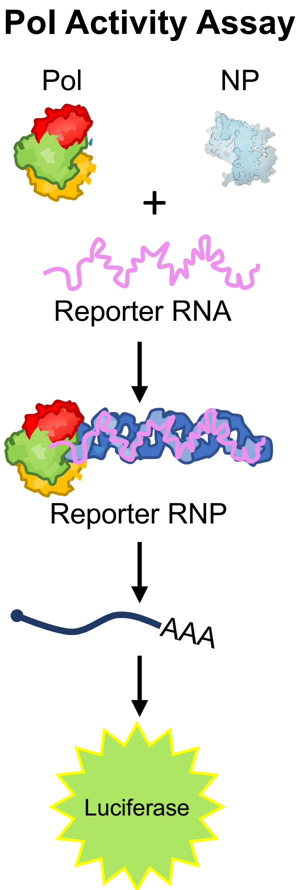
# Phosphorylation of NP maintains a monomeric state

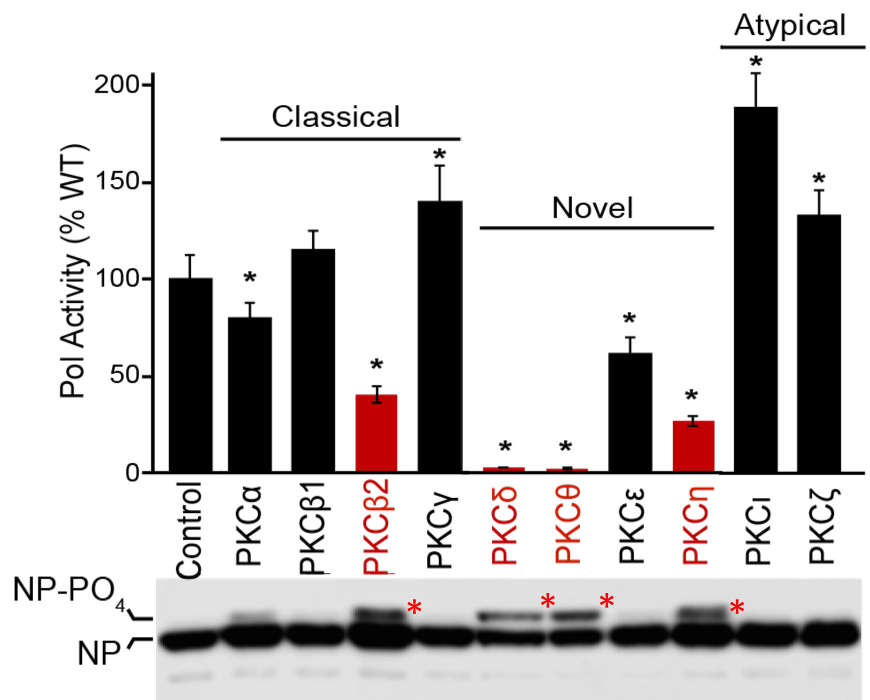



**Do PKCs phosphorylate NP and regulate viral RNA synthesis?**

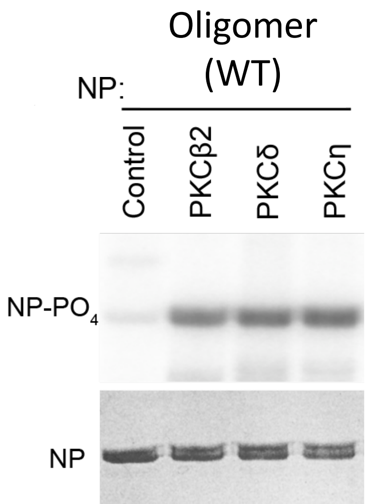
Mondal *et al*, PLOS PATHOGENS 2015; Hutchinson, et al. 2012; Chenavas, et al. 2013

# Constitutively active PKC isoforms alter polymerase activity

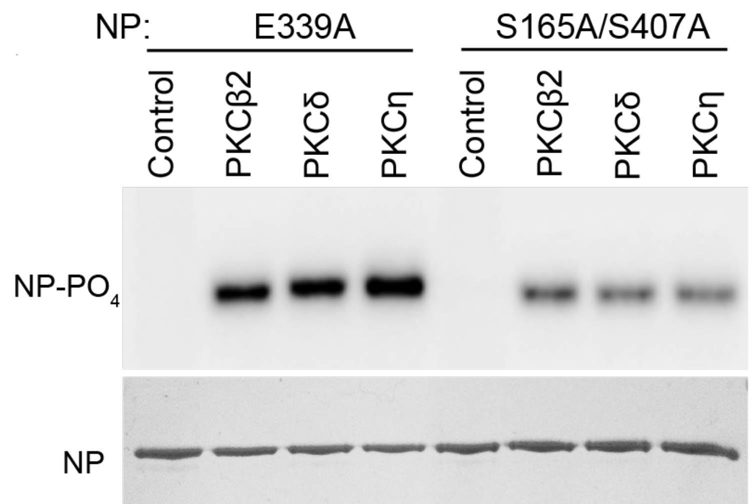


# PKC phosphorylates NP S165 and S407 *in vitro*



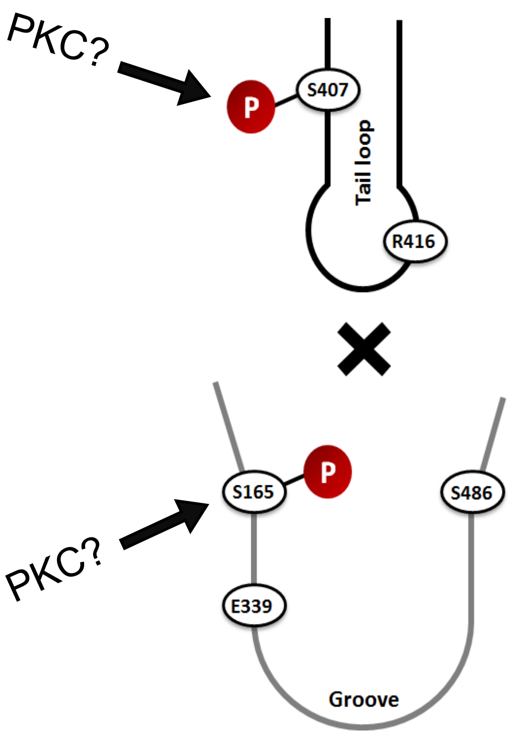

Phospho-sites occluded in NP oligomer



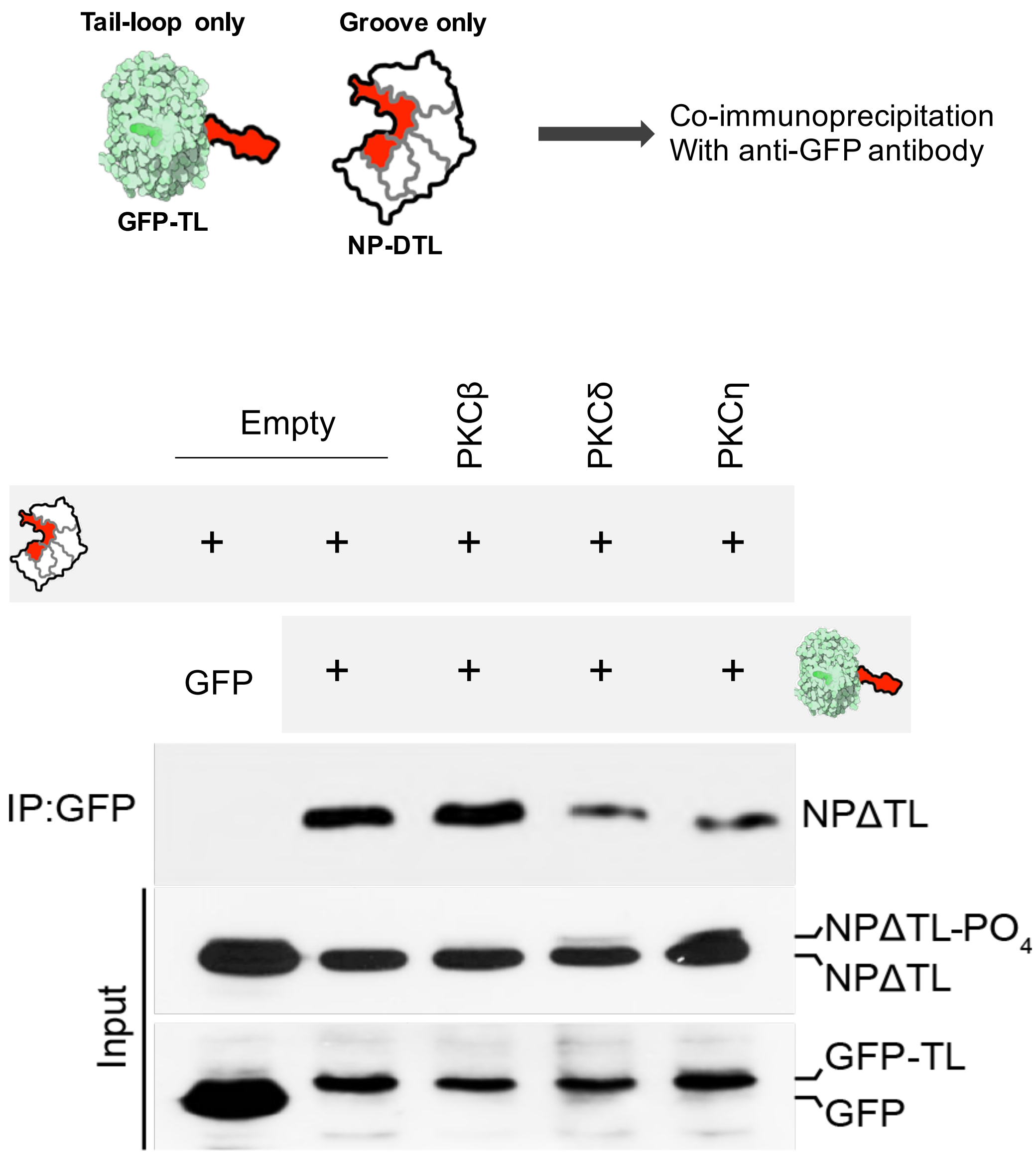

NP S165 and S407 are PKC targets

*In vitro* kinase assays with purified PKC and NP

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

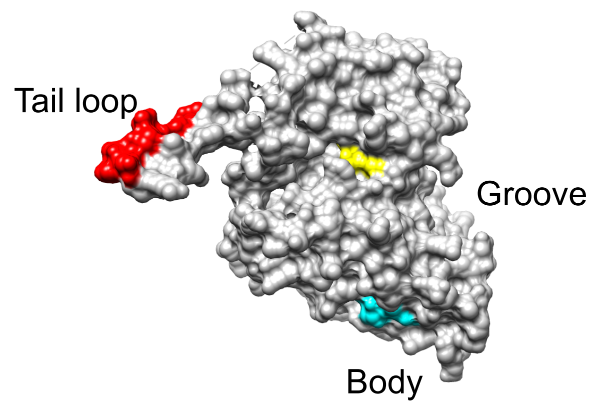


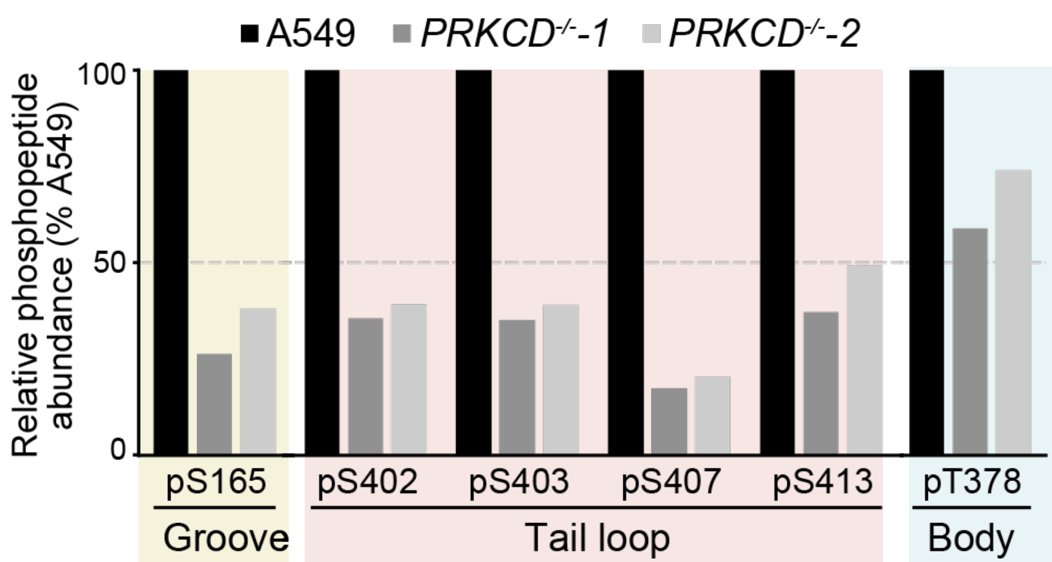

Tail loop:groove interaction assay



# Knockout of PKCδ reduces NP phosphorylation and replication

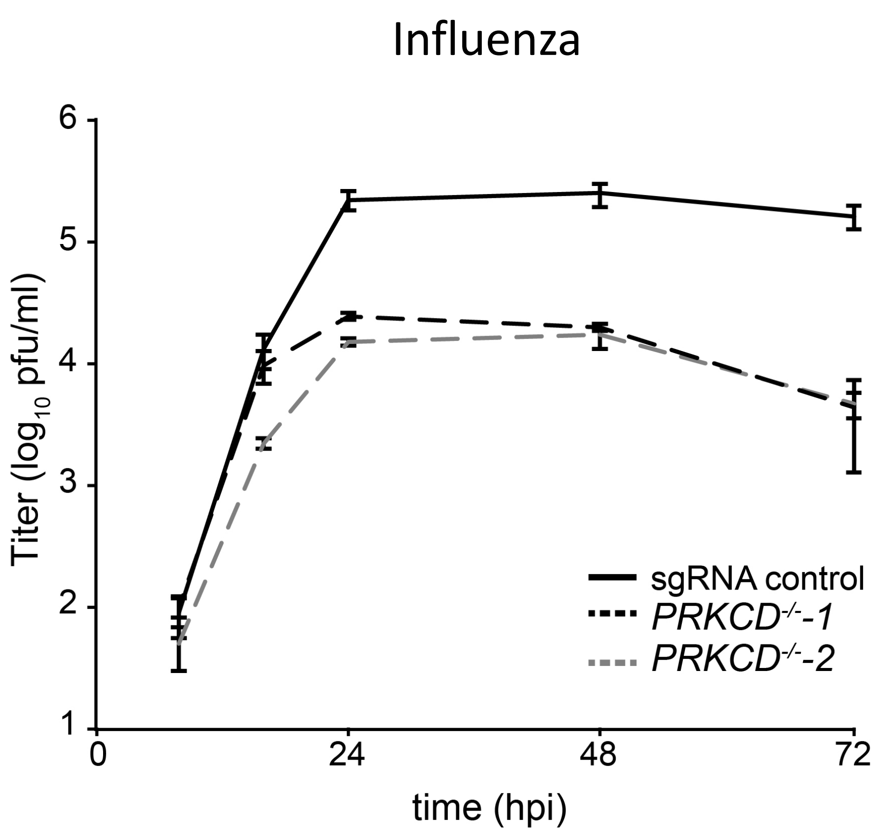
## Quantitative mass spectrometry analysis

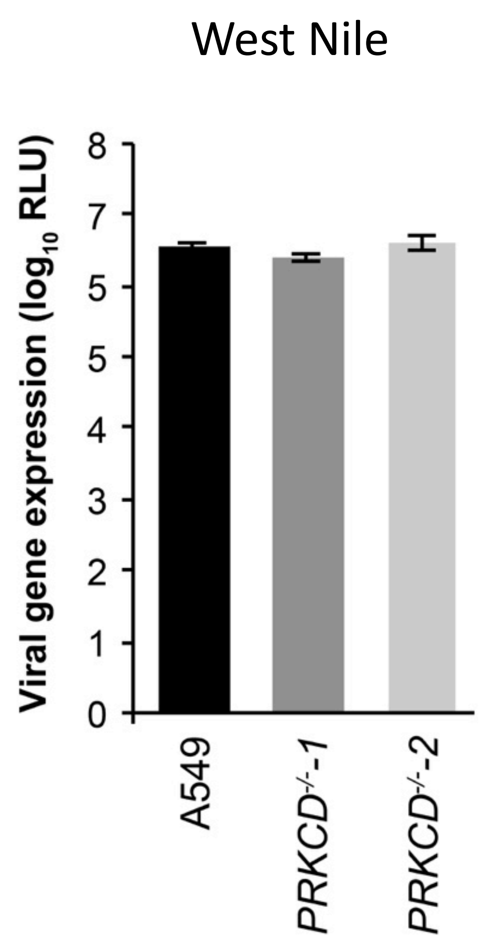


# Knockout of PKCδ reduces NP phosphorylation and replication

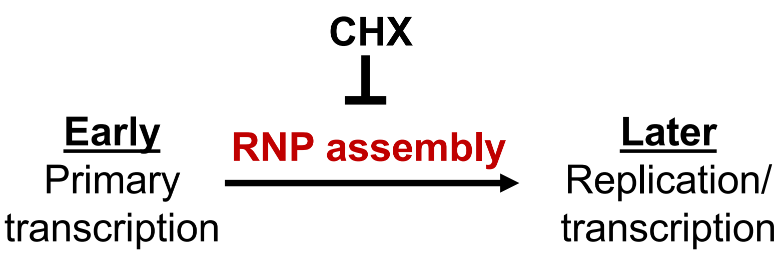
## Viral replication

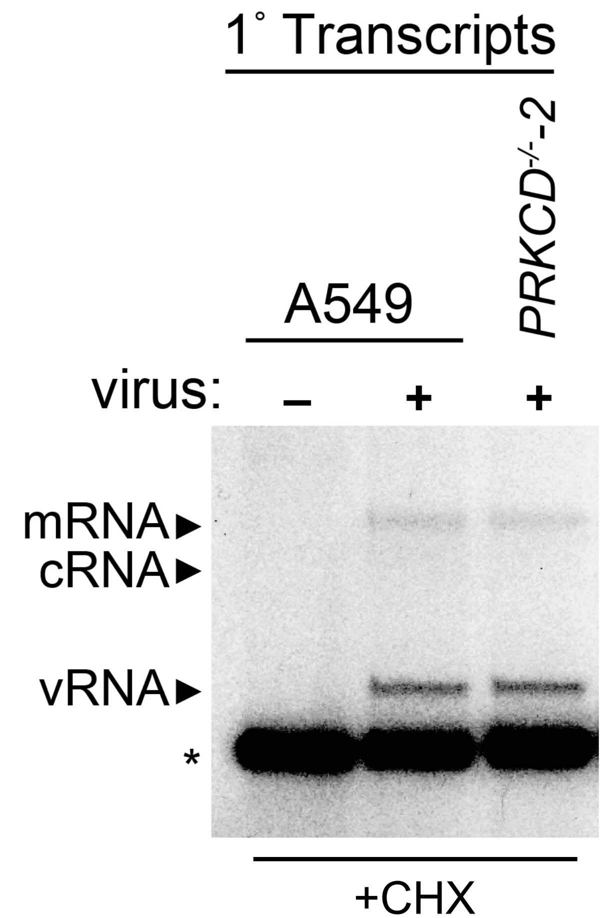



in collaboration with Kristen Bernard and Lindsey Moser

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



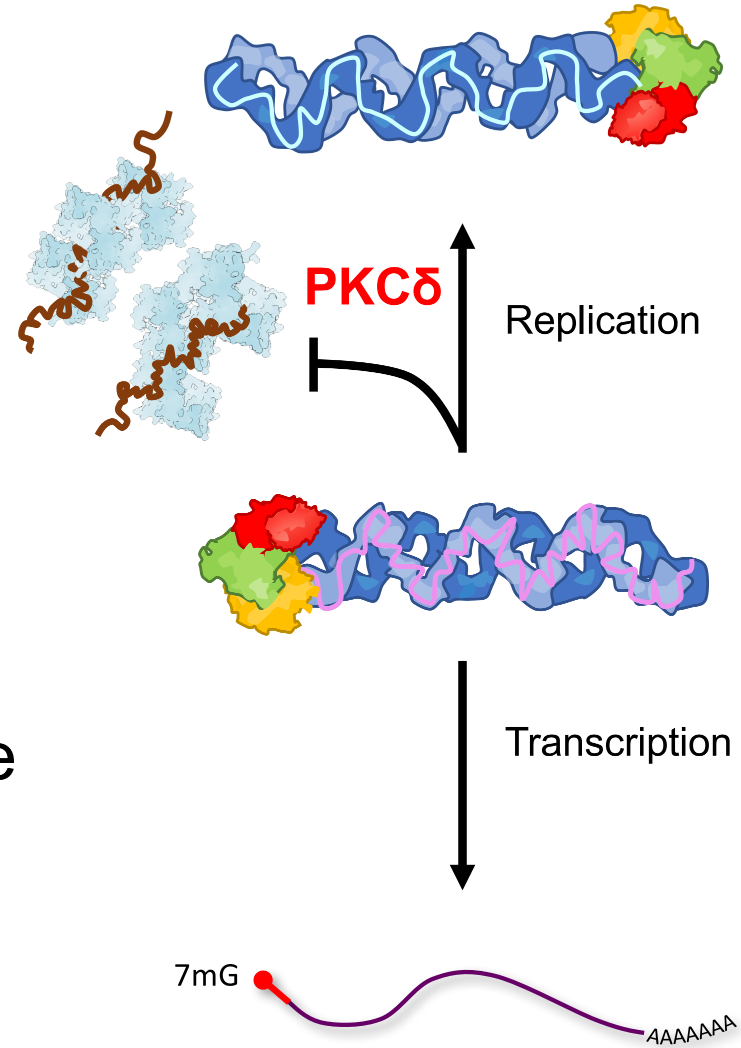




acid-bypass infection

# PKCδ creates a pool of RNP-competent NP

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

*What licenses RNP assembly?*
*Phosphatase?*
*How is NP recruited and where is it incorporated?*



We know a lot.

There is a lot we don't know, yet.

amehle@wisc.edu

slides at

**RNAi:** AATK, ABCB10, ABCC10, ABCC6, ABCD1, ACACA, ACE2, ACOX1, ACP2, ACRC, ACSL1, ACSL4, ACTC1, ACTL6B, ACTN2, ACVR1C, ACVR2A, ADAM8, ADAMTS1, ADAMTS2, ADAMTSL4, ADAT1, ADCY7, ADRA1B, ADRB2, ADRBK2, AFF2, AGTRAP, AHCY, AHCYL1, AHNAK2, AHR, AIG1, AKAP11, AKAP13, AKT1, AKT3, ALAS1, ALG10, ALG6, ALPK2, AMHR2, AMMECR1, AMN, AMOTL1, AMOTL2, ANAPC2, ANGPTL3, ANKK1, ANKMY2, ANKRD7, ANKS6, ANPEP, AP2B1, AP2M1, APBA3, APBB1IP, APC, APC2, APOA1, APOA5, APOBEC3G, APOL6, APP, APPBP1, AQP4, AQR, ARAF, ARCN1, ARD1, ARL4A, ARMCX5, ARNT, ARTN, ASAH1, ASPA, ATCAY, ATF1, ATF2, ATF4, ATG16L1, ATP13A1, ATP1A2, ATP1A3, ATP2C1, ATP5B, ATP5C1, ATP5F1, ATP5I, ATP6AP1, ATP6AP2, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V0E2, ATP6V1A, ATP6V1B2, ATP6V1G1, ATP8, AXIN1, B2M, B3GALT2, B3GNT7, B4GALT2, BACE1, BACH2, BAIAP2, BAIAP3, BANP, BARHL2, BCAS2, BCL10, BCL3, BCR, BHLHB2, BID, BIRC1, BIRC8, BLNK, BMPR1A, BMPR1B, BMPR2, BRPF1, BRWD3, BST2, BTG1, BUB1B, BUB3, BZRAP1, C10orf57, C11orf60, C11orf82, C12orf47, C12orf5, 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ARHGEF40, ARL1, ARL8B, ARMC6, ARSE, ASPH, ATAD3A, ATG9A, ATL2, ATL3, ATP1A1, ATP1A3, ATP1A4, ATP2A2, ATP2B1, ATP2B4, ATP4A, ATP5C1, ATP5F1, ATP5H, ATP5J2 PTCD1, ATP5L, ATP5O, ATP6V1H, ATRIP, ATRN, ATXN10, ATXN7L3B, AUP1, B4GALT1, B4GALT4, BAG2, BAG3, BAG4, BAG5, BASP1, BAT1, BIRC6, BOP1, BRAT1, BRD8, BRSK1, BTAF1, BUB3, BYSL, BZW1, C14orf156, C14orf166, C16orf80, C17orf85, C18orf34, C19orf43, C19orf52, C20orf114, C6orf211, C7orf27, C7ORF50, C8orf33, C9ORF167, CA12, CAD, CALR, CALU, CAND1, CANX, CAPN1, ... 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TTF2, TTI1, TTN, TUBA1A, TUBA1C, TUBA3E, TUBA4A, tubB, TUBB2A, TUBB2B, TUBB3, TUBB4A, TUBB4B, TUBB6, TUBG2, TUBGCP2, TUFM, TXNDC5, U2AF2, UAP1, UBA1, UBA2, UBA5, UBA52, UBAC2, UBB, UBE2G2, UBIAD1, UBR5, UBXD8, Uchl1, ULF1, UGGT1, UGT1A1, UGT1A6, UGT1A9, UMPS, UNG, UQCRC1, UQCRC2, UQCRFS1, UQCRH, URB1, USO1, USP10, USP11, USP14, USP15, USP34, USP9X, USP9Y, UTP20, UXT, VCAN, VCP, VDAC1, VDAC2, VDAC3, VIM, VKORC1, VPRBP, VPS4A, wdr1, WDR11, WDR5, WDR61, WDR77, WRNIP1, XPO1, XPO4, XPO5, XPO7, XPOT, XRCC5, XRCC6, XRN2, YBEY, YBX3, YIPF5, YME1L1, YTHDF2, YWHAE, YWHAH, YWHAZ, ZC3H15, ZC3H18, ZC3H4, ZC3HAV1, ZCCHC8, ZFR, ZNF281, ZNF346, ZNFX1, ZW10, ZWILCH **Luc complementation:** AAAS, ACSL4, ADAM21, AGFG1, AMIGO3, APOOL, BANP, BLZF1, C10orf96, C14orf166, C1orf94, CACNG7, CALCOCO1, CALCOCO2, CD274, CEP70, CLIC4, CMTM5, CNTN2, COPB2, CRYAB, DBH, DDX19A, DDX19B, DDX3X, DDX5, DOCK8, DPYSL2, DVL2, DVL3, eIF4E, FBXO40, FFAR1, FXR2, GABPB1, GABRB2, GLE1, GSTA2, GSTT1, GYPA, hnRNPM, HOOK1, HSP90AA1, IPO4, IPO5, KCNRG, KPNA1, KPNA2, KPNA3, KPNA5, KPNA6, LBR, LNX2, LRRC28, MAGEA11, MAGEA6, MDP1, MMP12, MVP, MYO1C, NCKIPSD, NCRNA00246B, NFE2L1, NHEDC1, NPM1, NRF1, NUP155, NUP160, NUP35, NUP50, NUP54, NUP62, NUP62CL, NUP93, NUPL1, NUPL2, NUTF2, NXF1, NXPH1, NXT1, OR2B6, PABPC1, PLEKHA9, PLVAP, PNMA1, POLR2A, POM121, PTGES3, PTPRE, RAB11A, RABGEF1, RACGAP1, RAN, RANGAP1, RBM15B, RBPMS, RHBDD2, RUVBL2, SAA2, SEMA3C, SENP2, SIAH1, SLC7A13, SNUPN, SPINK1, TACC1, TCF12, TFCP2, TOP3B, TRAF1, TRAF2, TRIP6, TRPT1, UBE2I, UGT3A1, USHBP1, VISA, XKR6, XPO7, ZNF131 **Y2H:** ACTB, C14orf166, CCHCR1, CHD6, CIAO1, CNRIP1, COPS5, CSRNP3, DCTN1, DRG1, EIF3S6IP, EIF4A2, FANCG, GOLGA2, GPR89A, IK, KAZR, KLC1, KLC4, LRRFIP1, LZTS2, MLH3, MNAT1, MYBL1, NBR1, NKX2 2, NMI, NNAT, NUP54, PARL, PCBD1, PCBP1, PITPNA, PLEKHG3, POLR2A, PPP1R12C, PRKRA, RANBP9, RC3H1, TAB2, TM7SF3, TNRC6A, TPR, USP22 **shRNA:** AB12, ABCB10, ACOT2, ACVR1B, ADAM11, APOBEC3G, ARRDC3, ATF1, ATG5, ATP6AP1, ATP6V0C, ATP6V1B2, ATP6VOD1, AXL, B3GAT1, BAD, BPTF, BRCA1, BTC, BUB1, C11ORF71, C13ORF28, C17ORF85, C1ORF56, C1QL3, C4BPA, C4ORD35, C6ORF136, C6ORF162, C6ORF57, CAMK1, CCNJL, CD200R1L, CDH26, CDKN1A, CEBPG, CENPH, CENPK, CFL1, CHMP2A, CLECL10A, CLOCK, CMTM1, COX5B, COX7B2, CRNN, DAPK2, DCLRE1C, DDX3Y, DLAT, DOCK5, DPPA2, DR1, DSG4, DYRK1A, EED, EGFR, EIF2B1, EOMES, ERCC4, FBXO15, FBXO8, FMO2, FSHB, GAPDH, GAS2, GC, GIGYF2, GJC1, GON4L, GPR151, GULP1, HACE1, HCG_1986447, HIST1H1B, HIST1H2AB, HPS4, HRAS, HSPA8, HTR7, IFIT2, IFLTD1, IGF2BP1, IL17A, IL22, INPP4A, IPP, ITCH, ITGAM, ITGAX, IVNS1ABP, KCNJ16, KIAA0174, KIAA1751, KIF24, LARP6, LHX8, LOC339766, LOC730139, LRRC39, LSP1, MADD, MAEA, MALT1, MAML3, MAN282, MAPK10, MAPK13, MAPK9, MDM2, MED29, MED6, MERTK, METAP1, MLLT11, MPG, MSH6, MX1, MX2, NCRNA00200, NDUFB3, NEK3, NMBR, NRG1, NUP214, NUP85, NUPL1, NXF3, OR2W1, OR52A1, OR52M1, P2RY12, PAB5A, PCDH12, PCDHA9, PDGFRA, PIK3C3, PLA1A, PLEKHH1, PLK4, POLD3, POLE2, POLR2J2, PQLC1, PSMD14, PTAFR, PTDSS1, PTGER2, PTPN13, PTPRJ, PYY, RAB7A, RABGAP1, RAD23A, RARS2, RBPJ, RCVRN, RIOK3, RIPK3, RLN1, RNF19A, RNF24, RPL23, RPS25, RRP1B, SAGE1, SCG2, SELPLG, SENP1, SERPINA1, SH3BP4, SIN3B, SIPA1, SLC20A1, SLC7A14, SLC7A4, SMARCE1, SMOC1, SMPD2, SNTB2, SP100, SPOCK2, ST8SIA3, STARD5, STX3, TAF4B, TAS2R16, TBC1D2B, TCFL2, TFPI2, TH1L, THOC6, TMC6, TMEM11, TMEM14A, TMTC4, TNFSF12 TNFSF13, TNFSF13, TNFSF9, TNRC6A, TPD52, TRIM13, TRIM16, TRIM16L, TRIM21, TRIM59, TTN, TXNDC16, UBXN7, UGT2B15, USP16, USP22, USP34, USP37, USP47, USP8, WNK2, WT1, XCR1, YPEL2, YWAH, YY2, ZCCHC14, ZCCHC4, ZFP2, ZNF251, ZNF397, ZNF71, ZSCAN12, ZSCAN16 **random_homozygous_insertion:** ADAM20, AKT1, ARID1B, CHM, COG5, COX5A, CSNK1D, DDX17, DDX58, GRK6, HEATR7A, HERC6, LRRC16A, LSM4, MDN1, MRPL42, N4BP2, NDUFA7, NDUFAF2, PKD2L2, RAD51L1, RHGP, SF3A3, SLC25A25, SLC30A9, STXBP1, VPS34, ZNF7 **haploid screen:** CMAS, SLC35A2