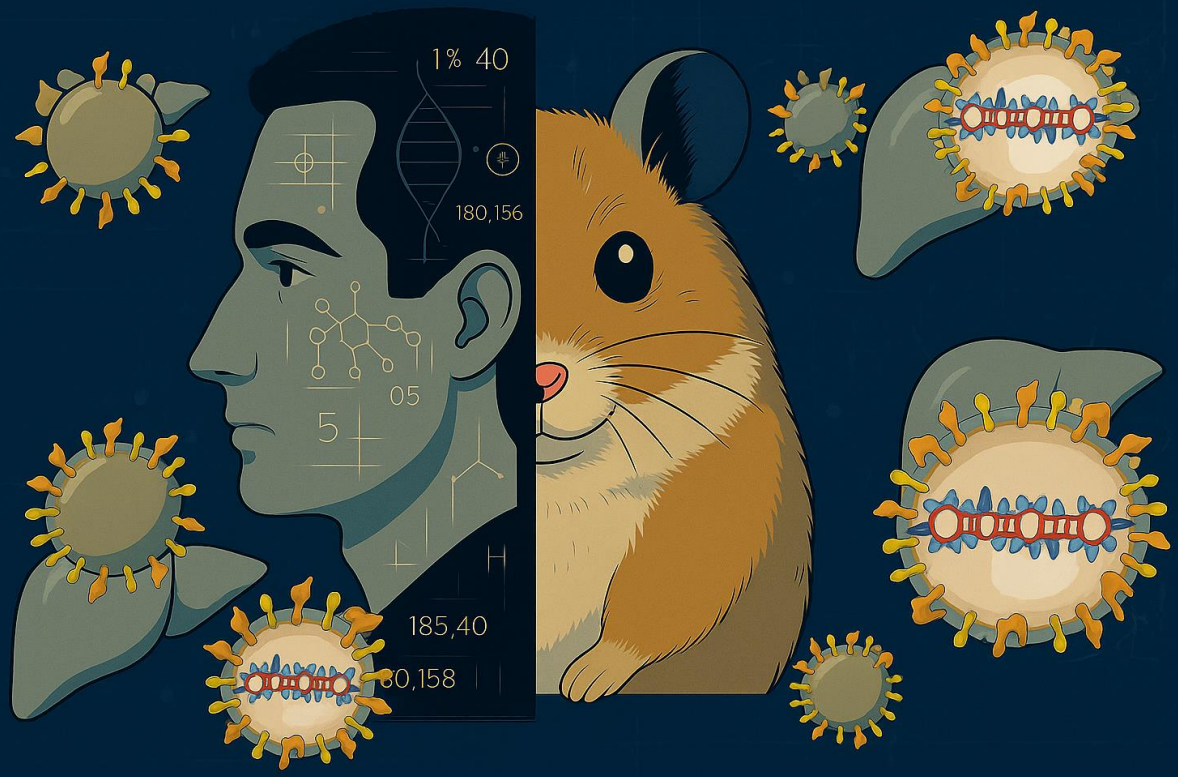


A Syrian Hamster Model of HDV Infection

Elias Broeckhoven, Felix Van Bavel, Maxime Smits, Lars Degrauwe, Madina Rasulova, Hendrik-Jan Thibaut, Lotte Coelmont, Yannick Debing, Chris Van Den Haute, Rik Gijsbers & Kai Dallmeier

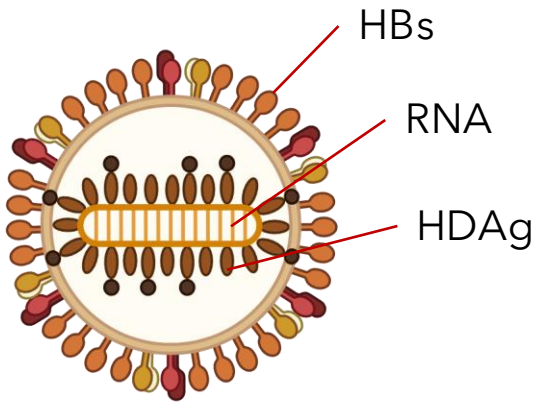
KU LEUVEN

MVVD

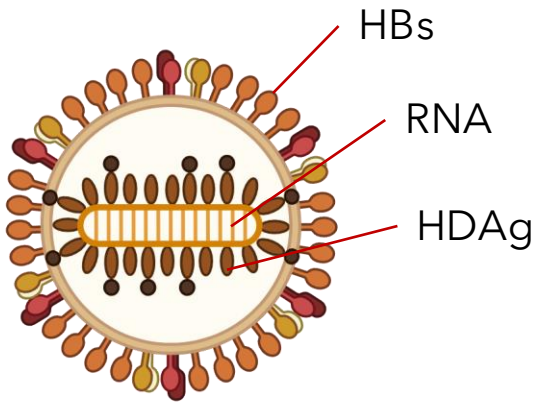
Molecular Vaccinology and Vaccine Discovery

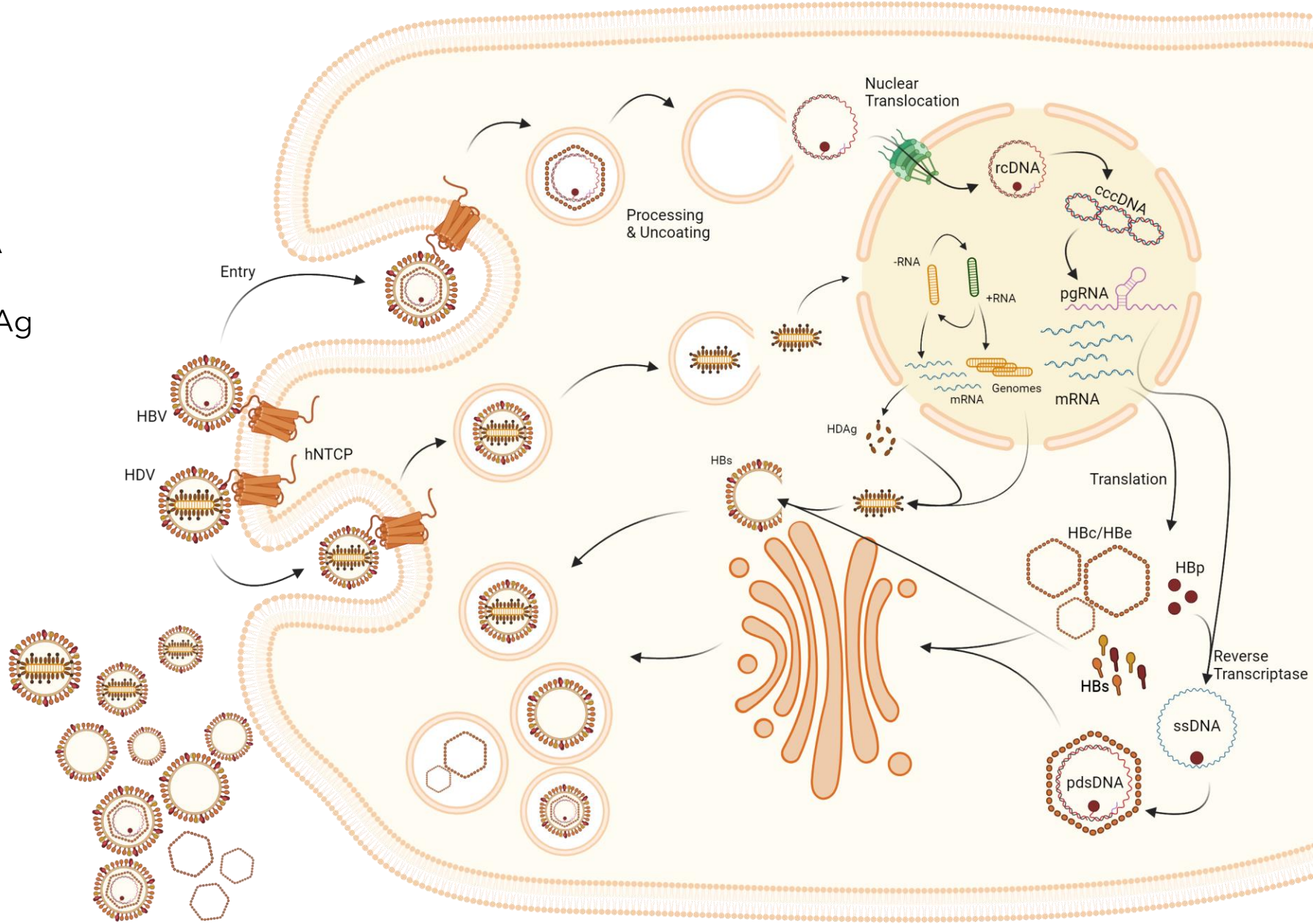
fwo

Hepatitis Delta Virus (HDV)

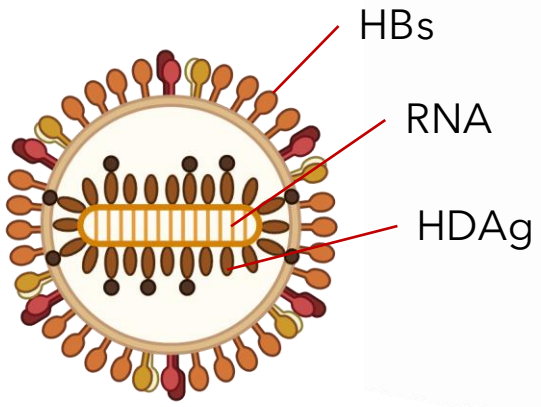


Hepatitis Delta Virus (HDV)





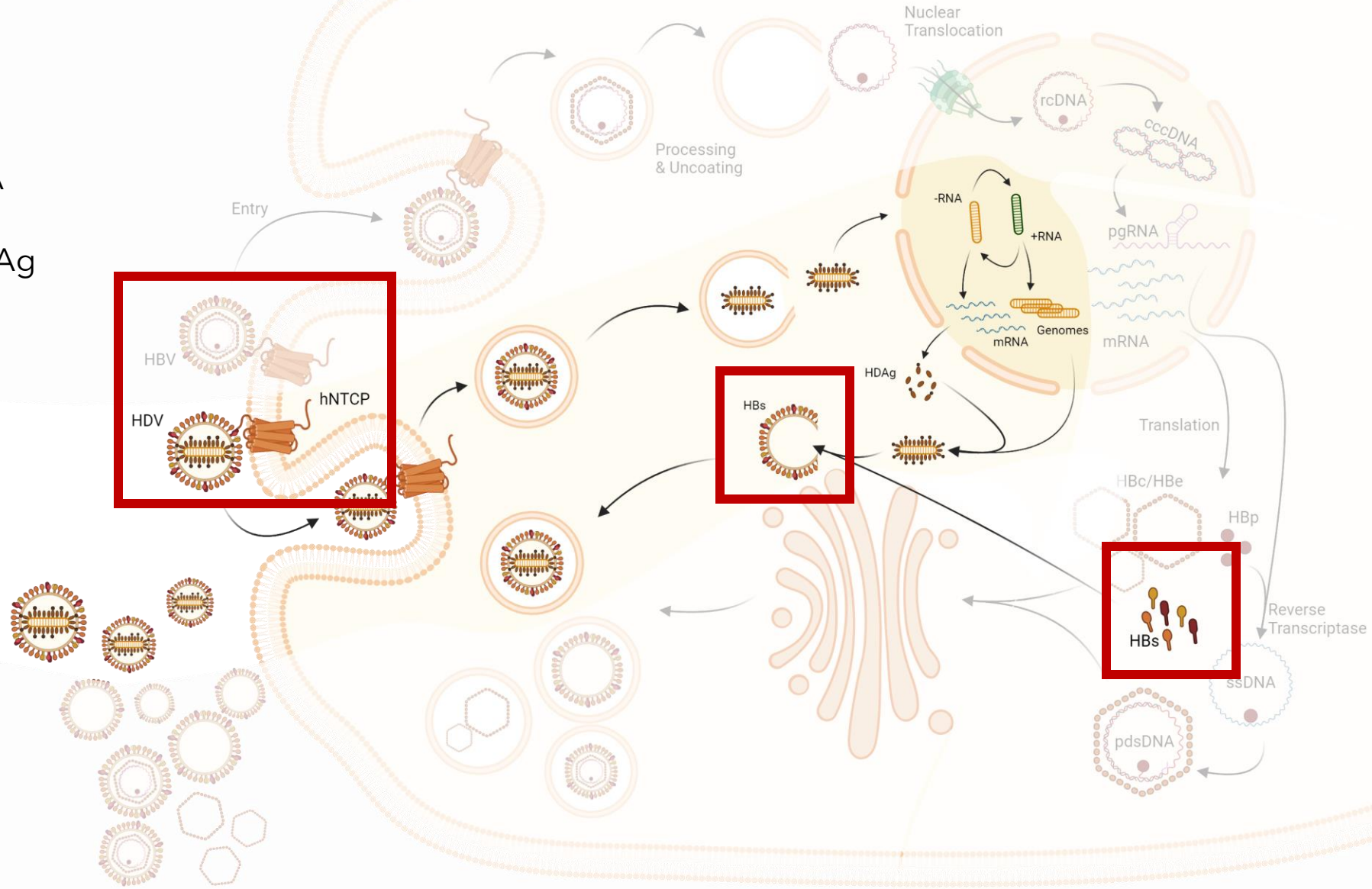
Hepatitis Delta Virus (HDV)



Requires HBV Enveloppe (HBs) as enveloppe

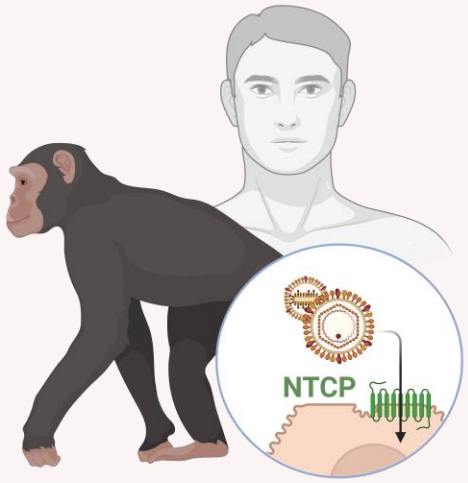
Same entry mechanism

hNTCP as bona fide entry receptor

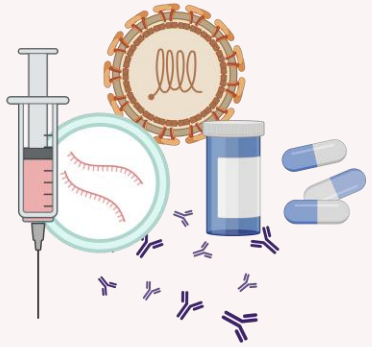


Models of HDV Infection

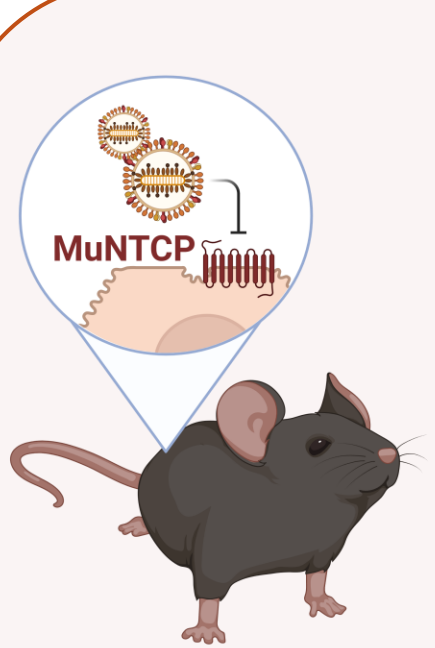
The Problem

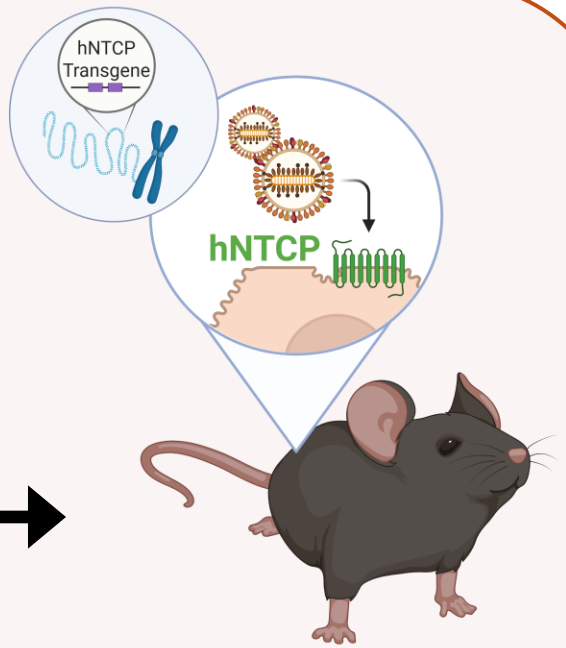


Therapy Development



The Compromise





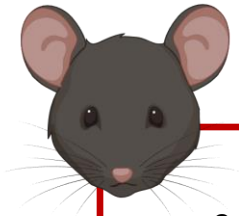
However

Require immunocompromised or neonatal status

Shortlived and suppressed infection

Need for new & improved models

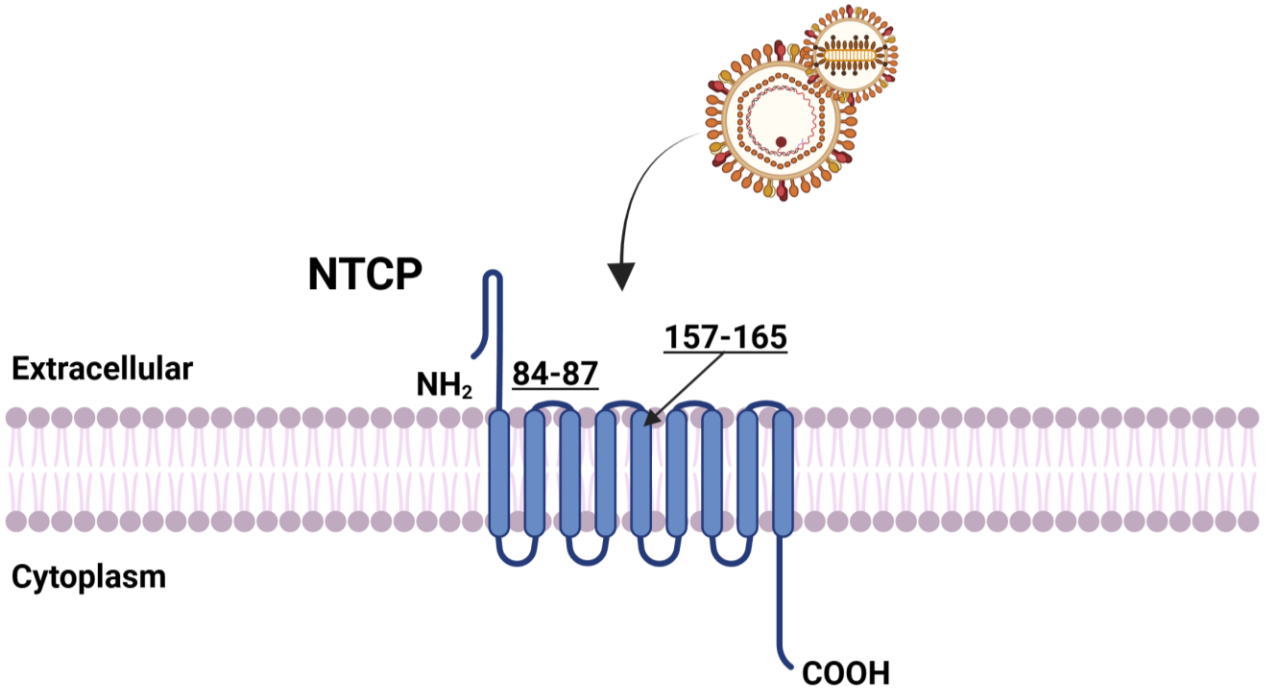
A Susceptible Hamster Model



hNTCP mouse model (SCID/Neonatal)

Low translational value
& limited ease-of-handling

hNTCP hamster model



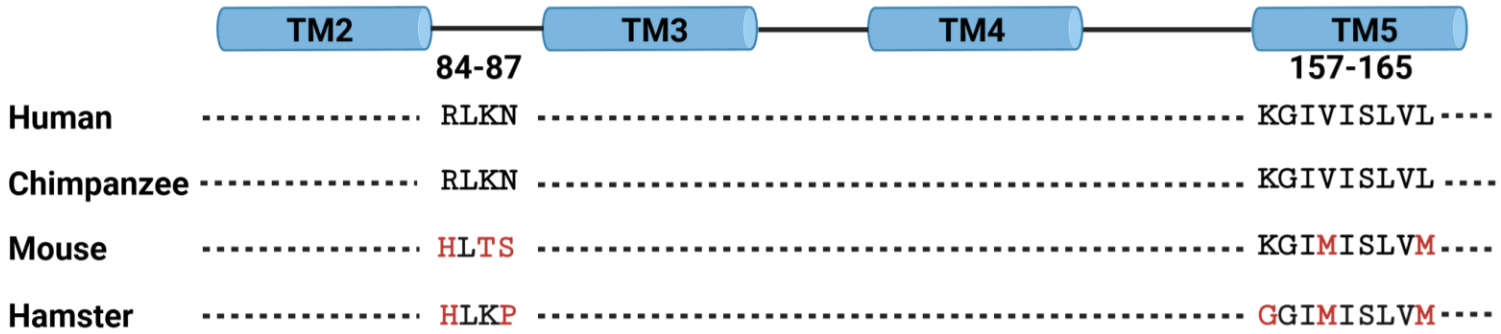
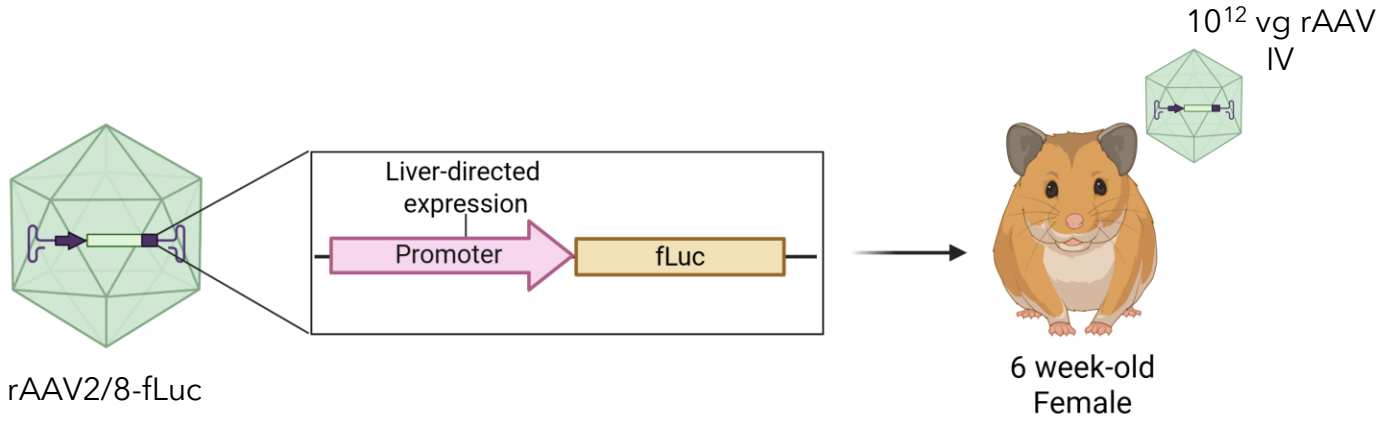
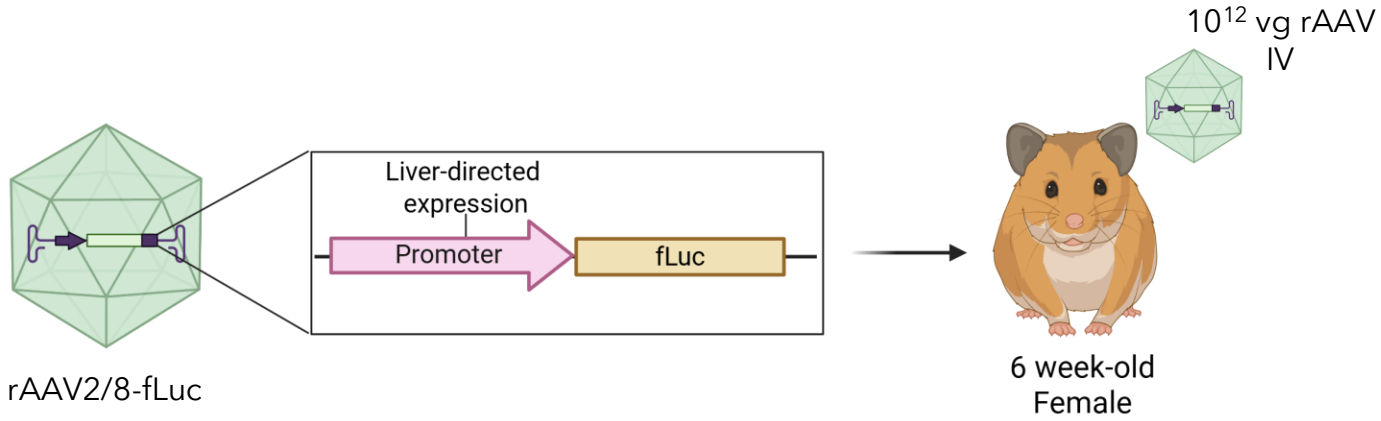


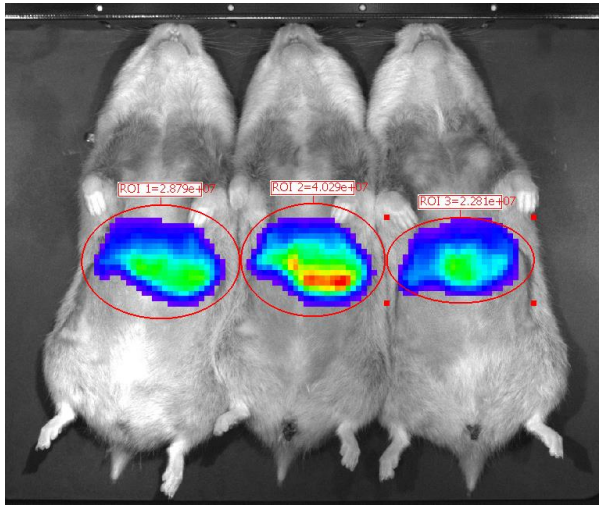
Image adapted from Zhang et al. (2024)

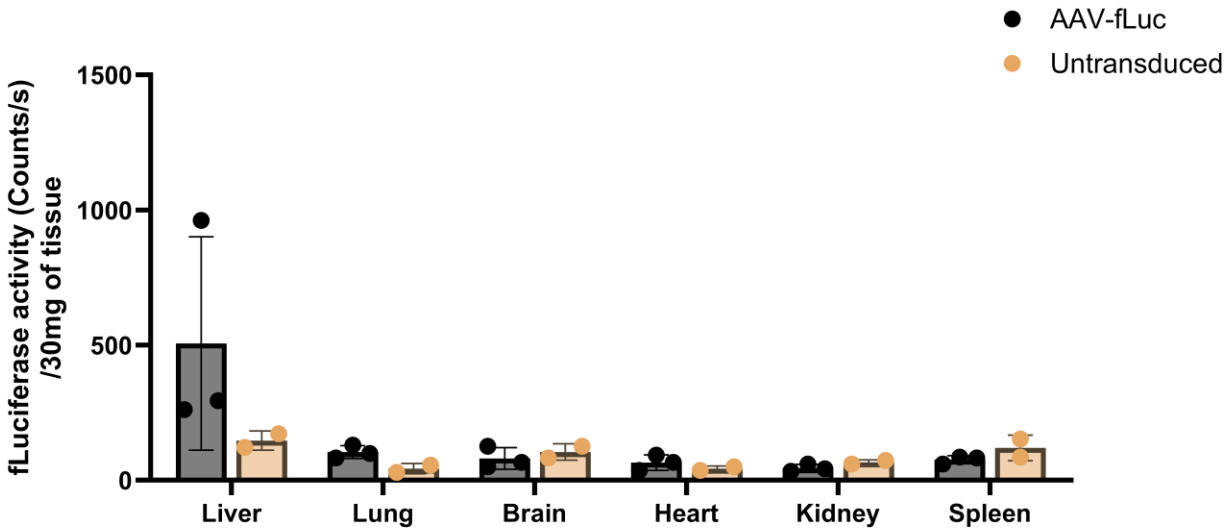
Liver-specific expression



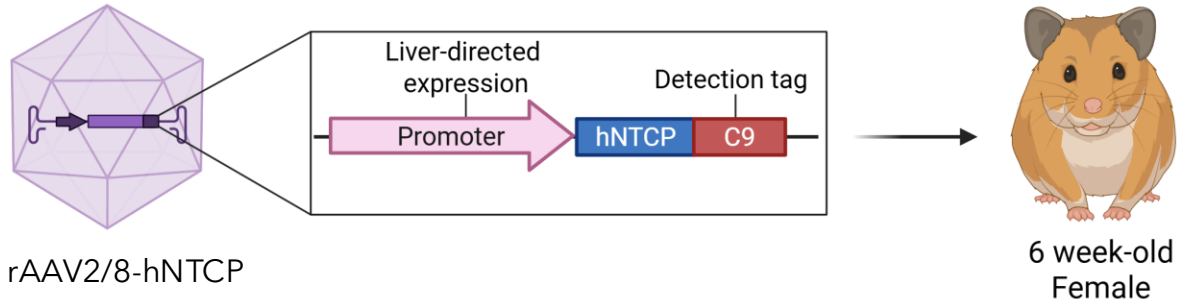
Liver-specific expression

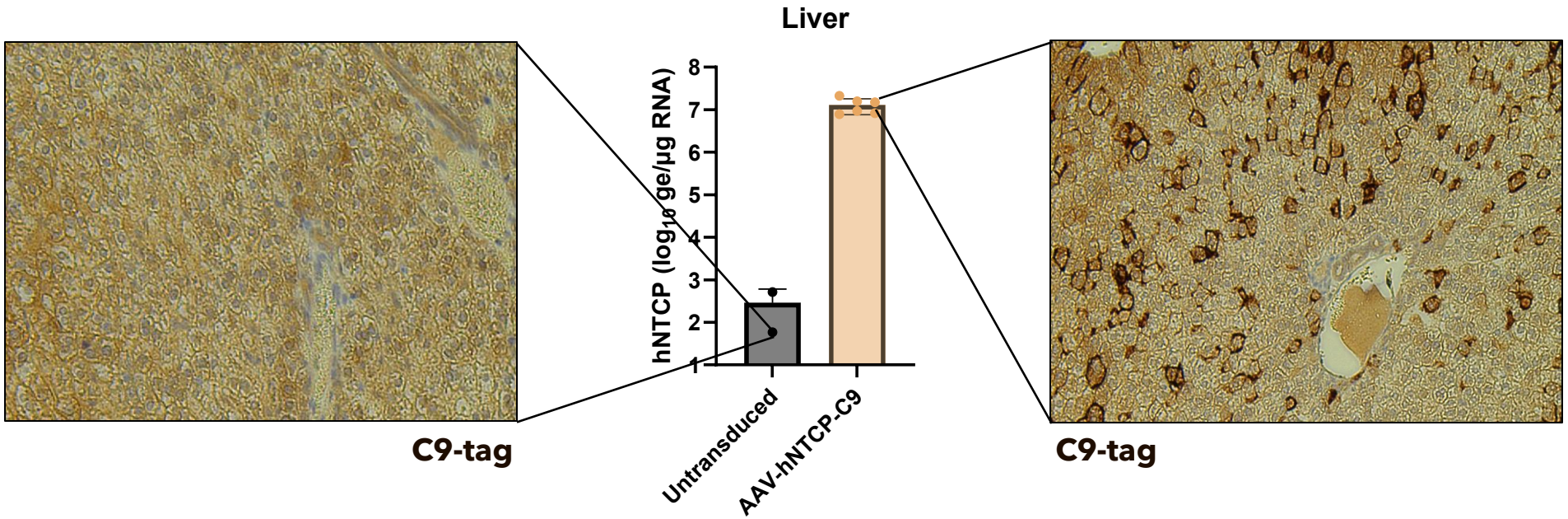




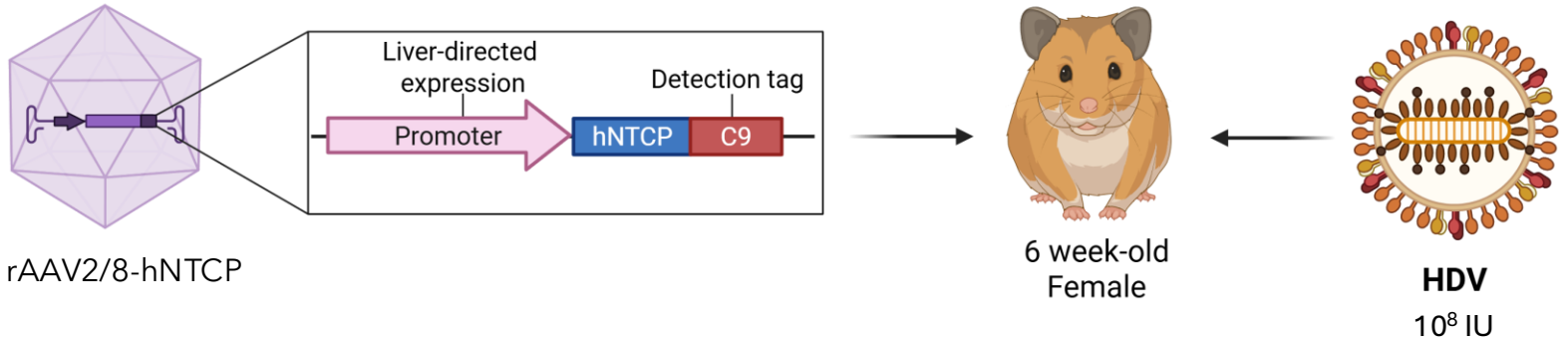


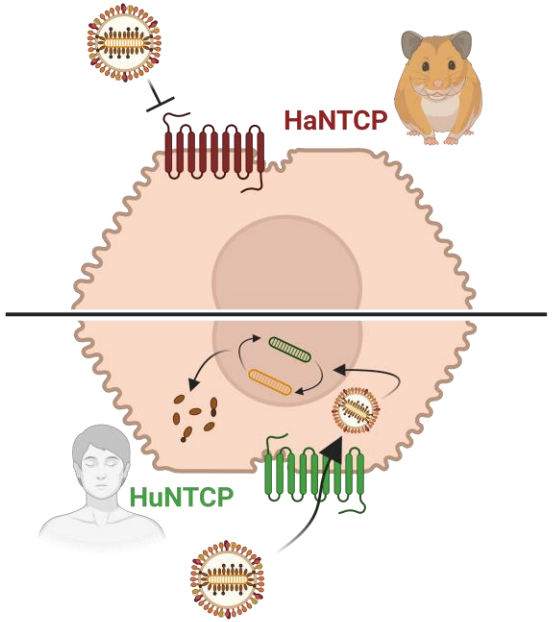
A hNTCP Hamster Model

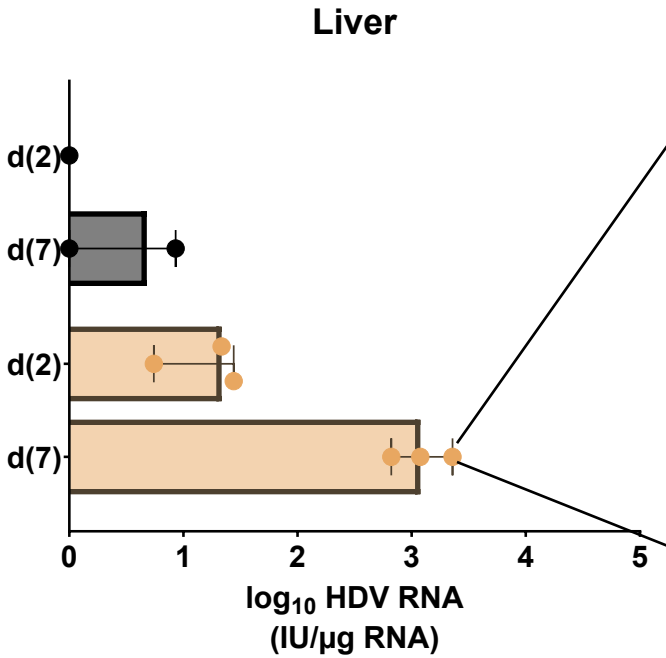


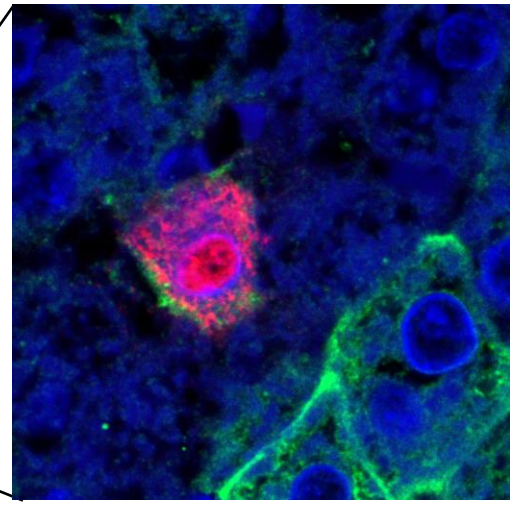


A Susceptible Hamster Model



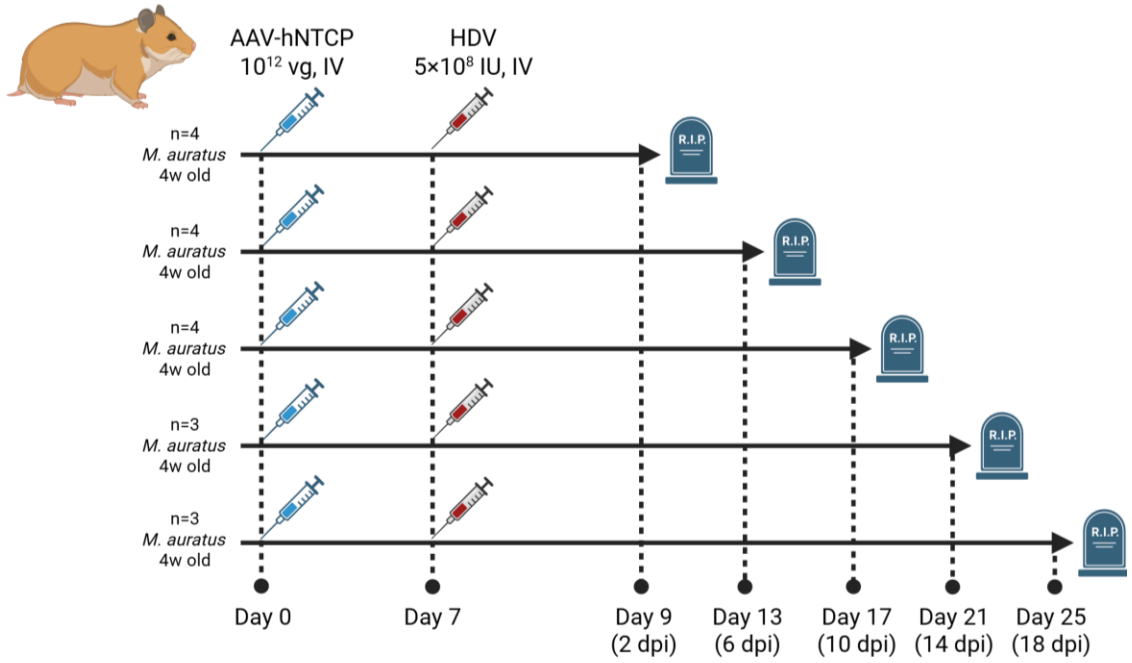




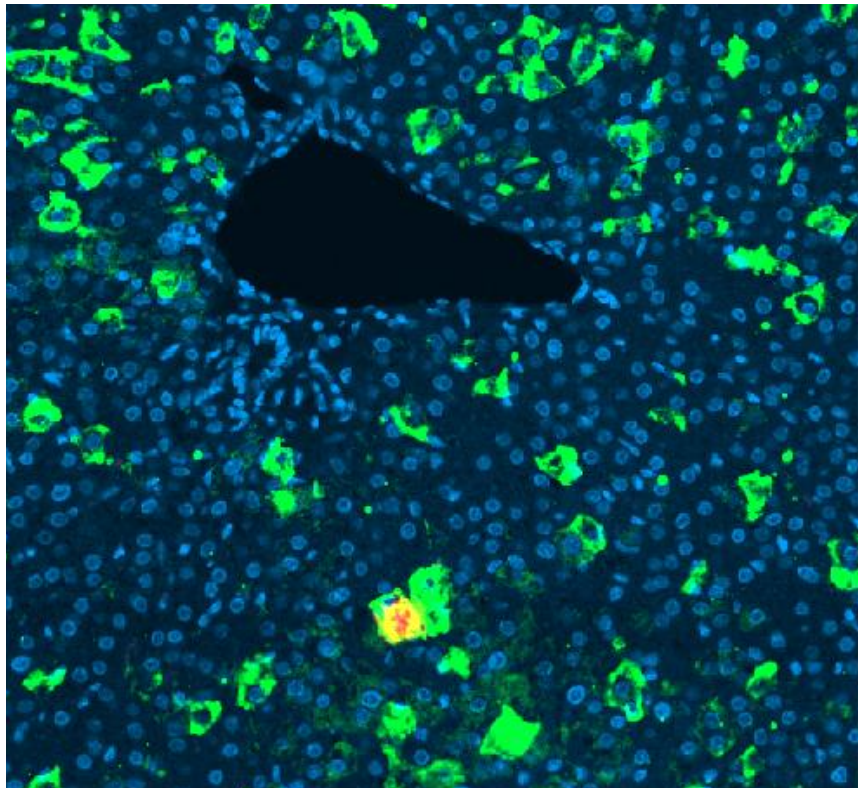


Nuclei
C9-tag
HDAg

Viral Kinetics

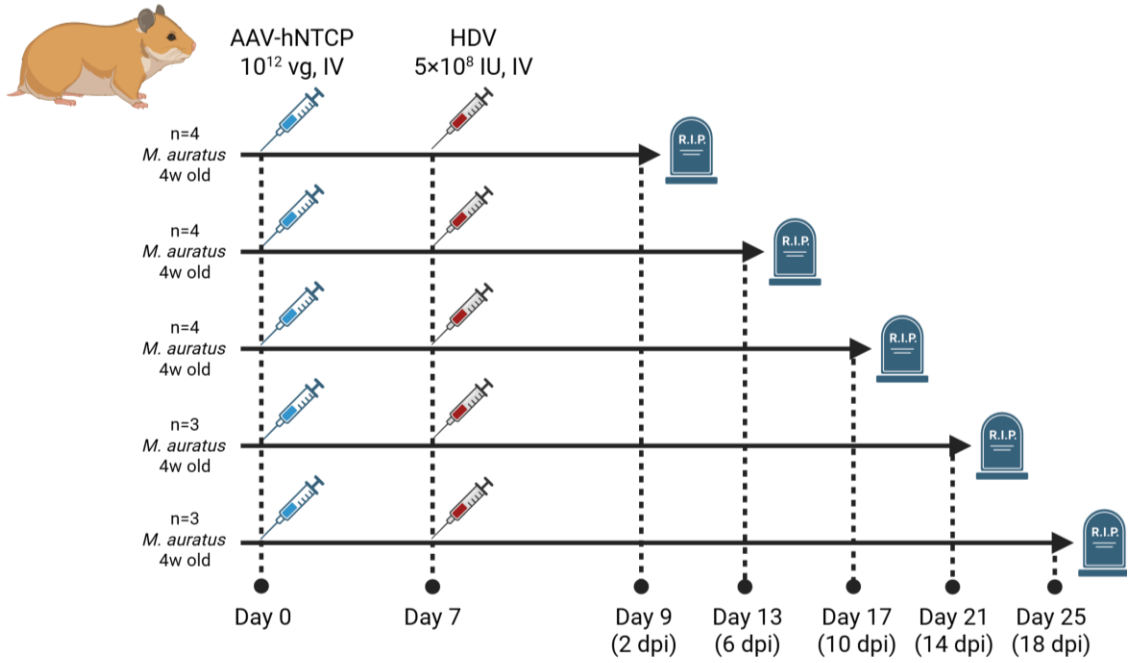


Liver

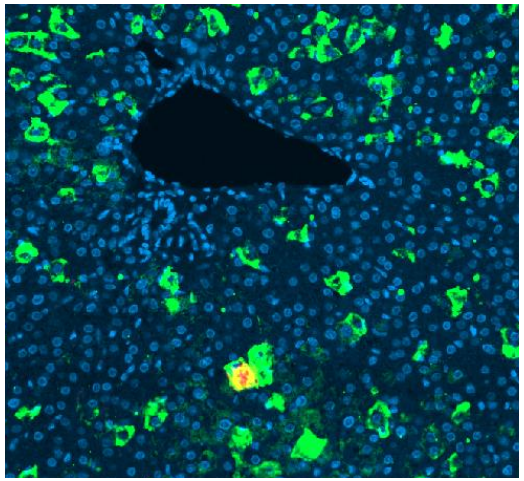


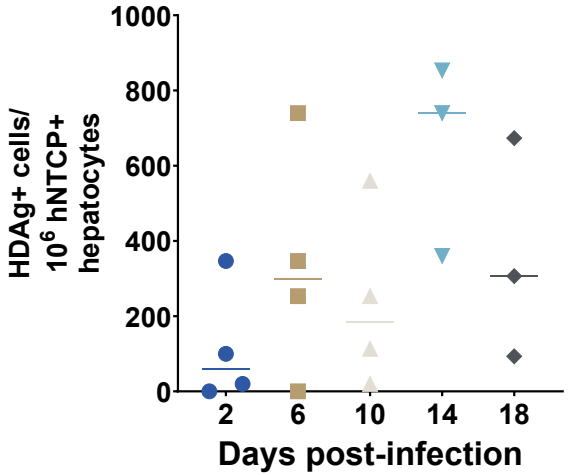
C9 (hNTCP)
Nucleus
HDAg

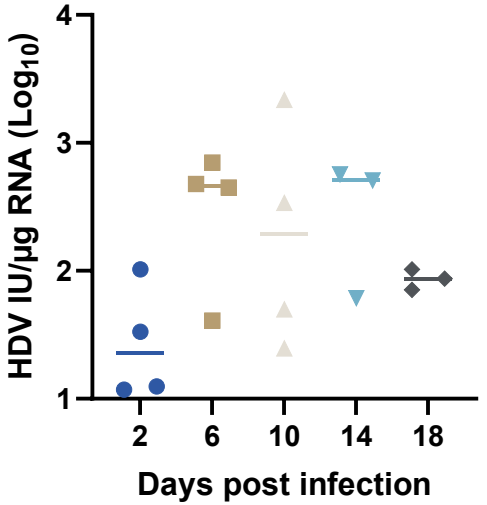
Viral Kinetics

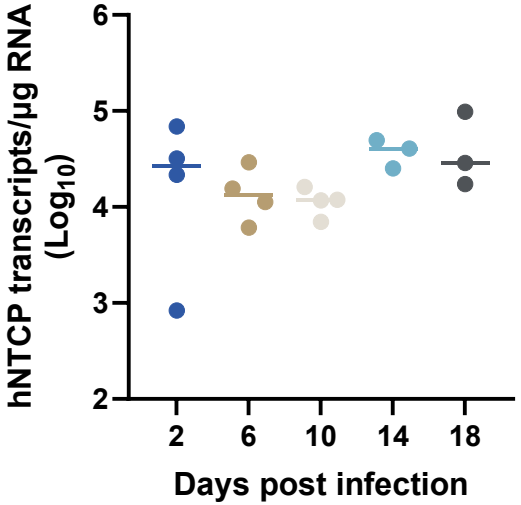


Liver

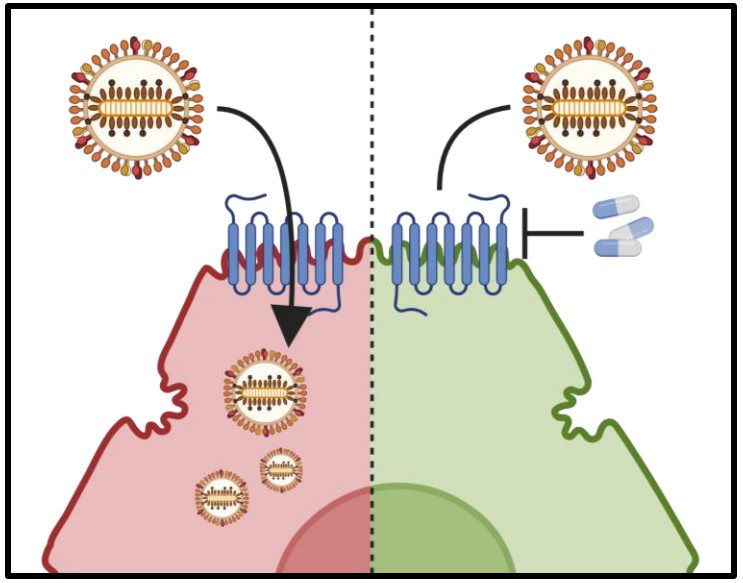


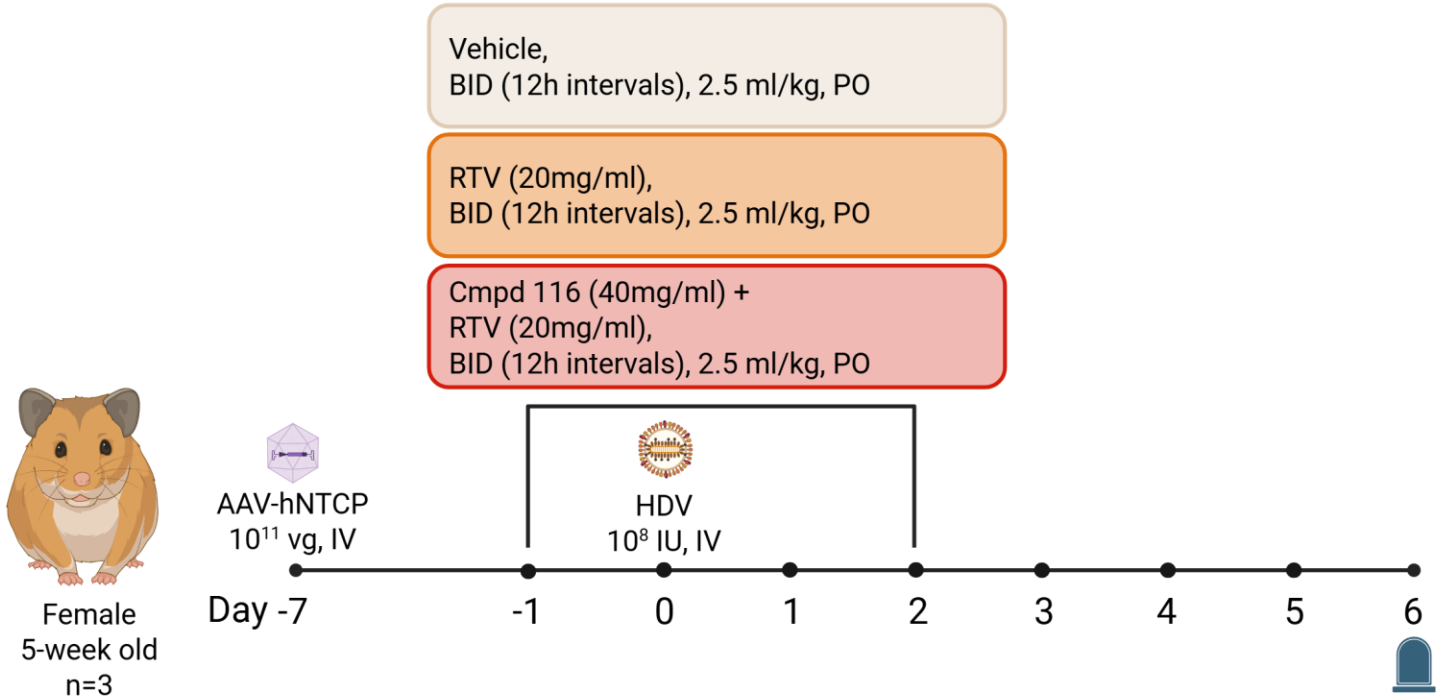






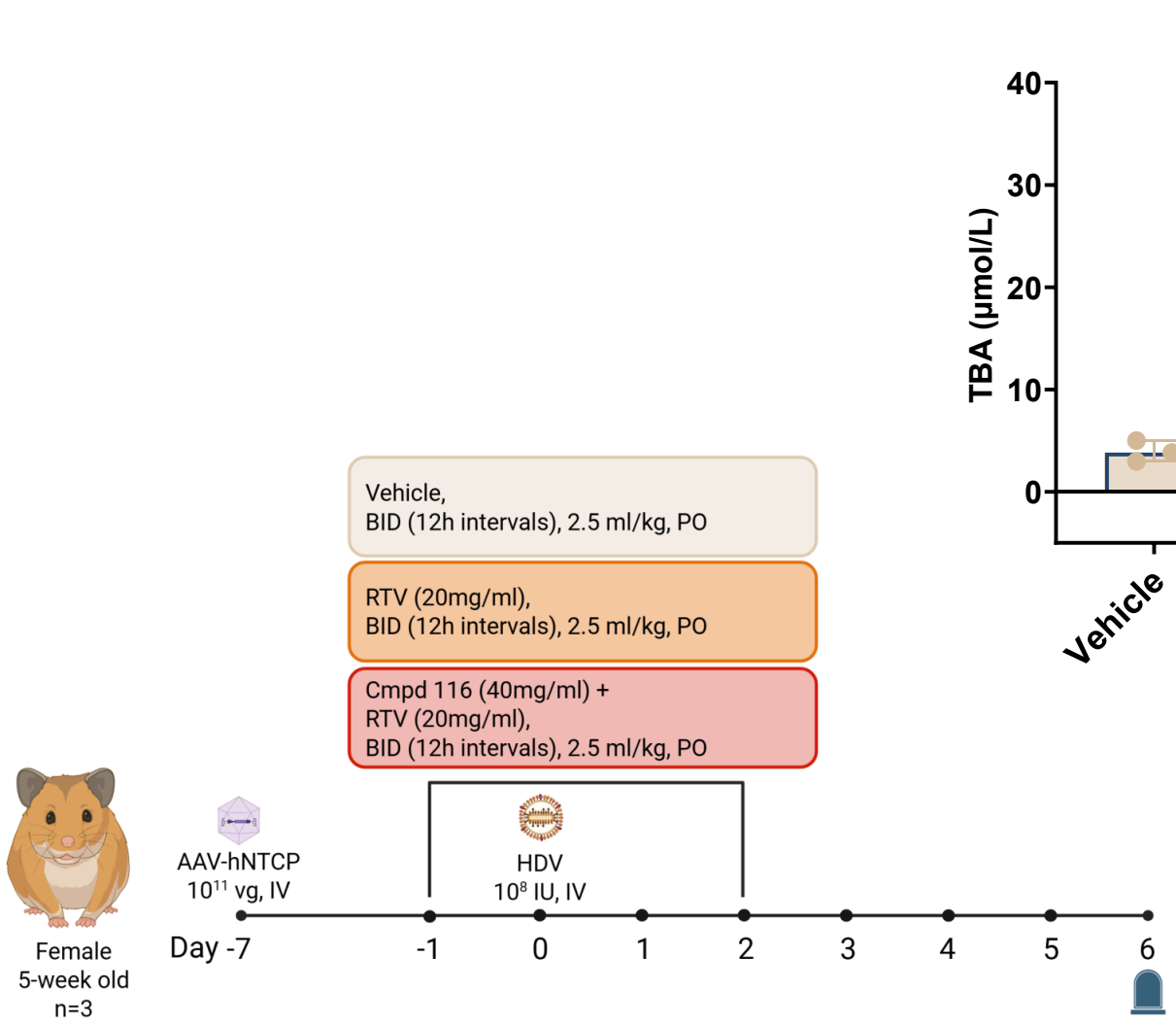
NTCP inhibitors block HDV infection

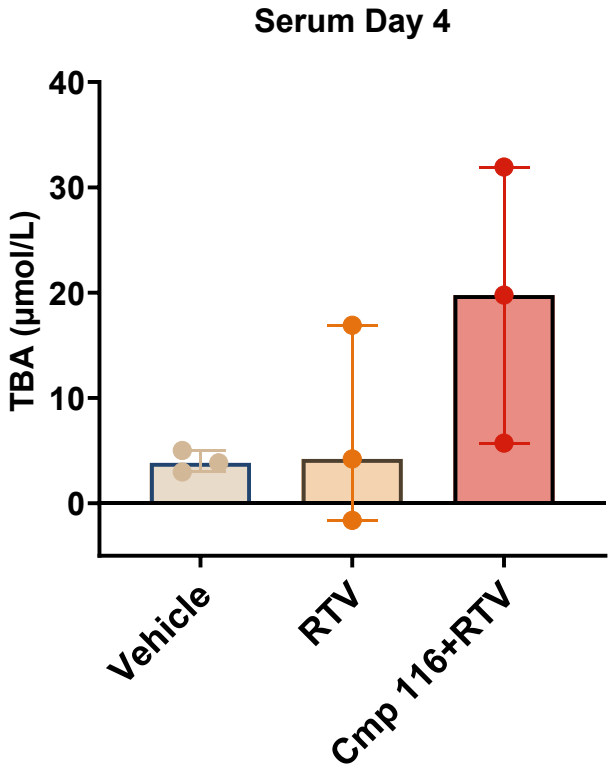


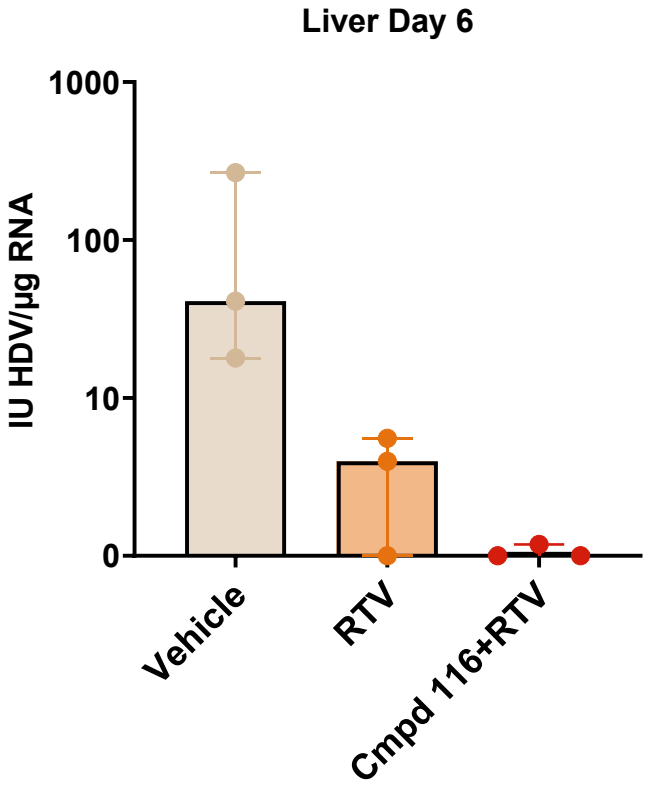


McRae M. P. et al., "*Ritonavir, Saquinavir, and Efavirenz, but Not Nevirapine, Inhibit Bile Acid Transport in Human and Rat Hepatocytes*", JPET (2006)
Bartlett S. et al., "*FUSED HETEROBICYCLIC ANTIVIRAL AGENTS*" (International patent WO2024044183)

NTCP inhibitors block HDV infection







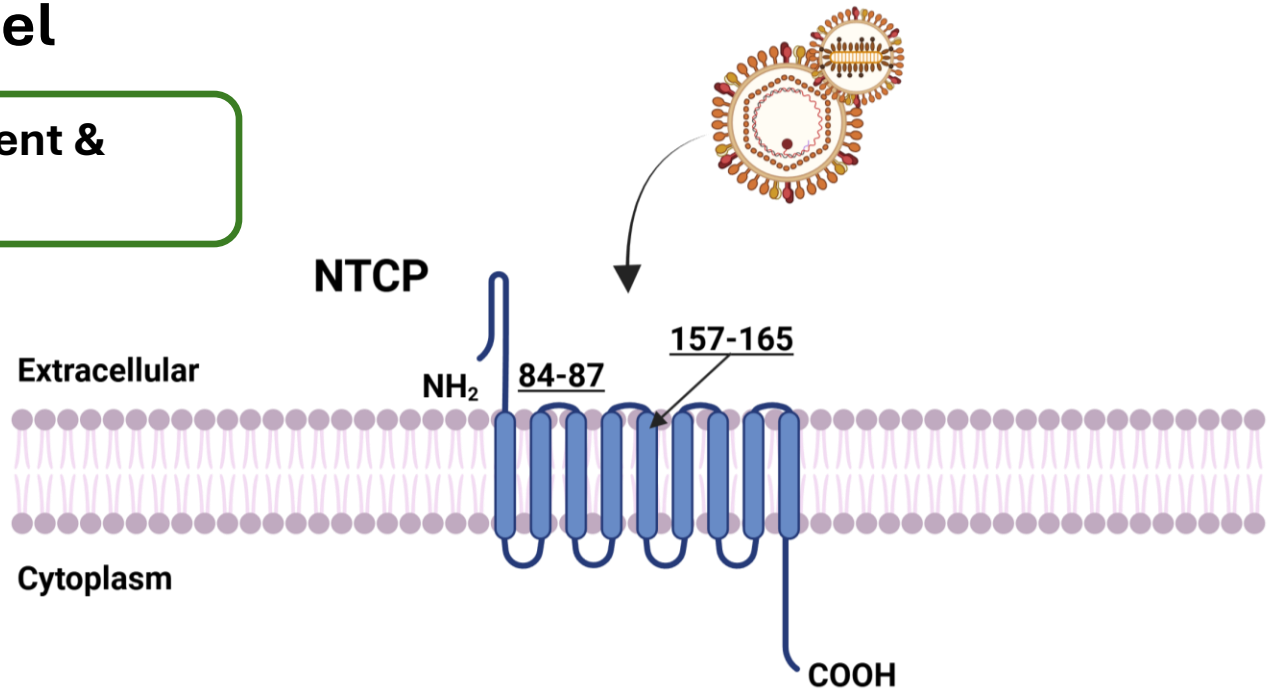
Oral combination therapy
NTCP inhibitor "116" & ritonavir
inhibits bile acid transport
& blocks HDV infection

McRae M. P. et al., "*Ritonavir, Saquinavir, and Efavirenz, but Not Nevirapine, Inhibit Bile Acid Transport in Human and Rat Hepatocytes*", JPET (2006)
Bartlett S. et al., "*FUSED HETEROBICYCLIC ANTIVIRAL AGENTS*" (International patent WO2024044183)

Humanizing the hamster NTCP

hNTCP hamster model

Susceptible, immunocompetent & persisting infection



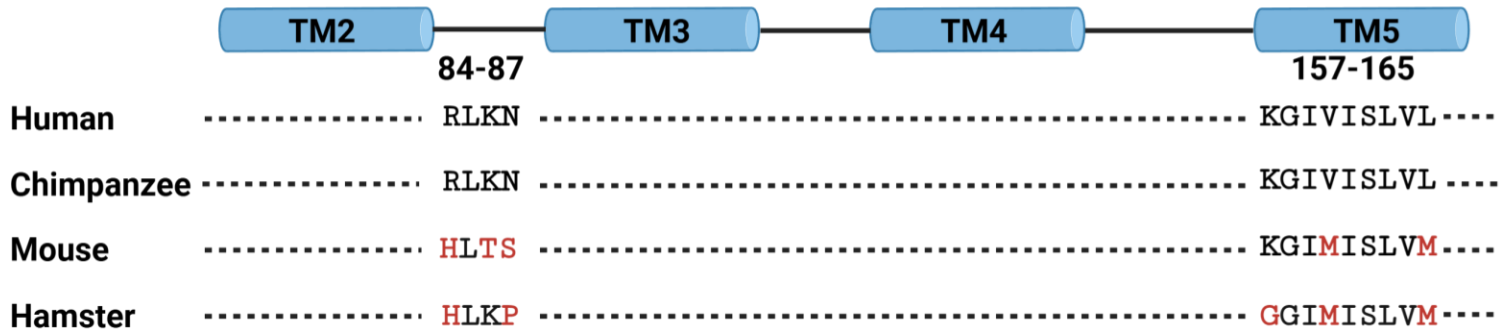


Image adapted from Zhang et al. (2024)

Humanizing the hamster NTCP

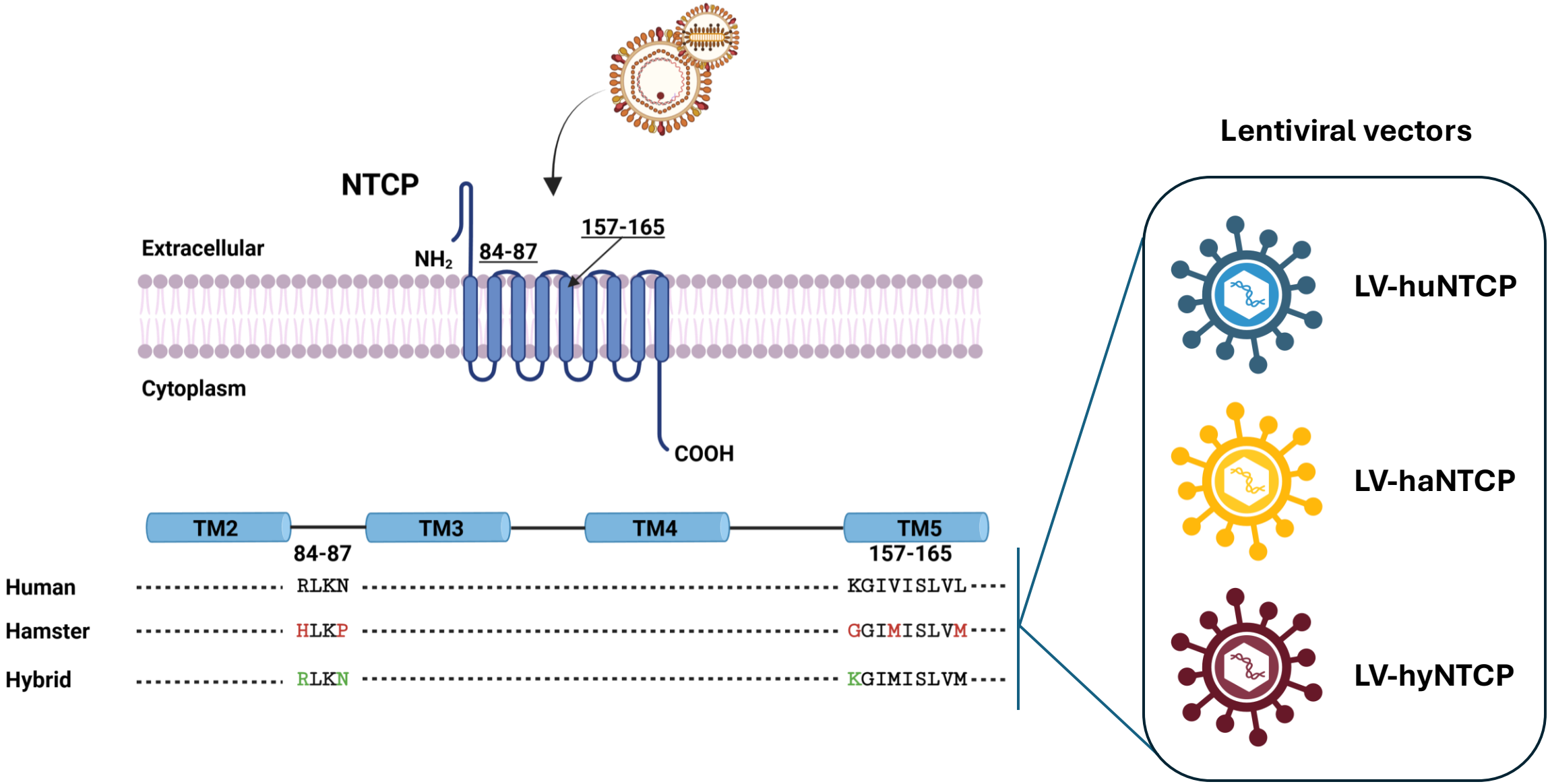
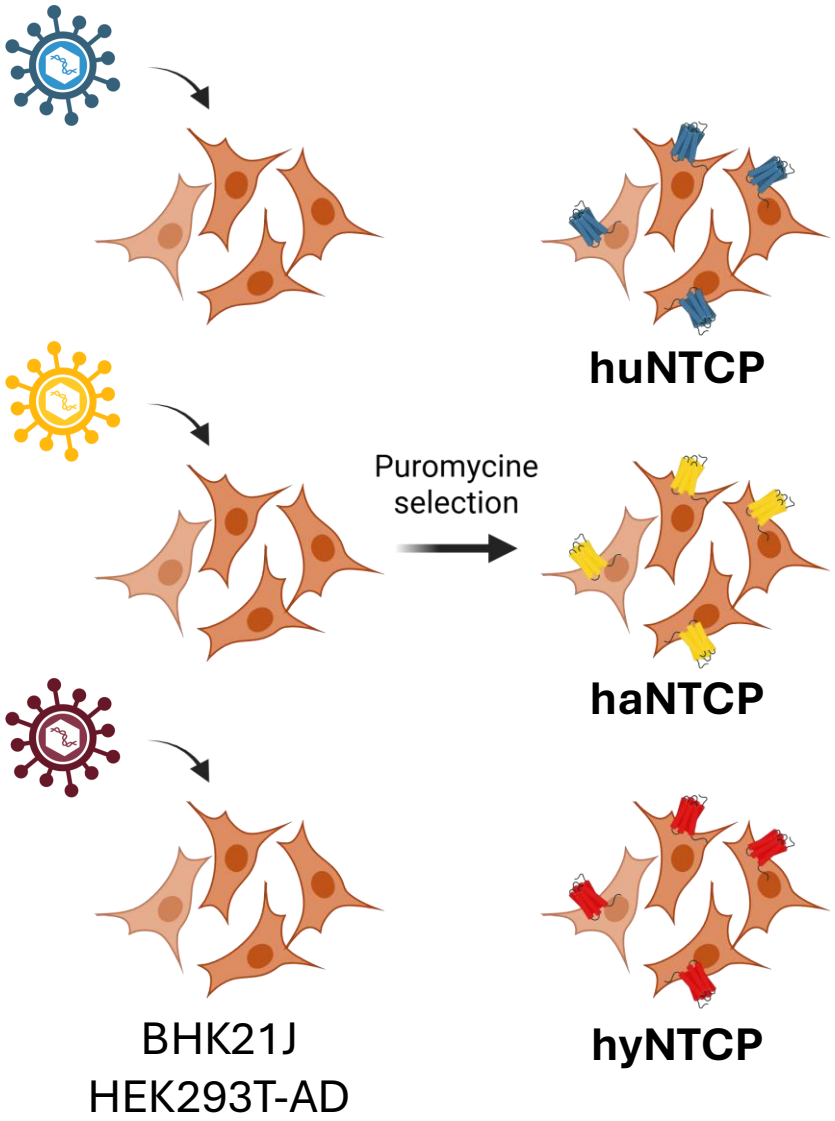
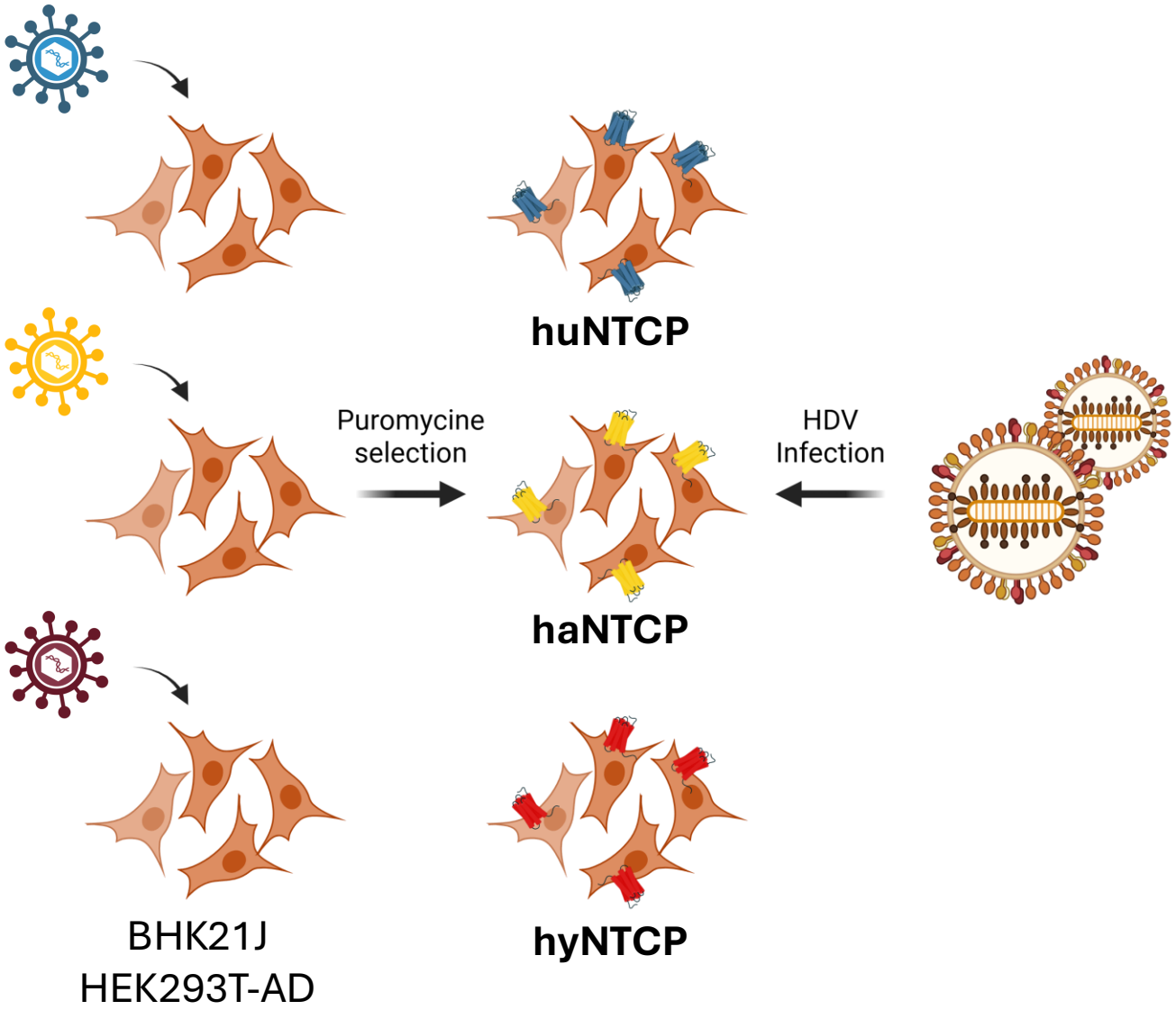


Image adapted from Zhang et al. (2024)

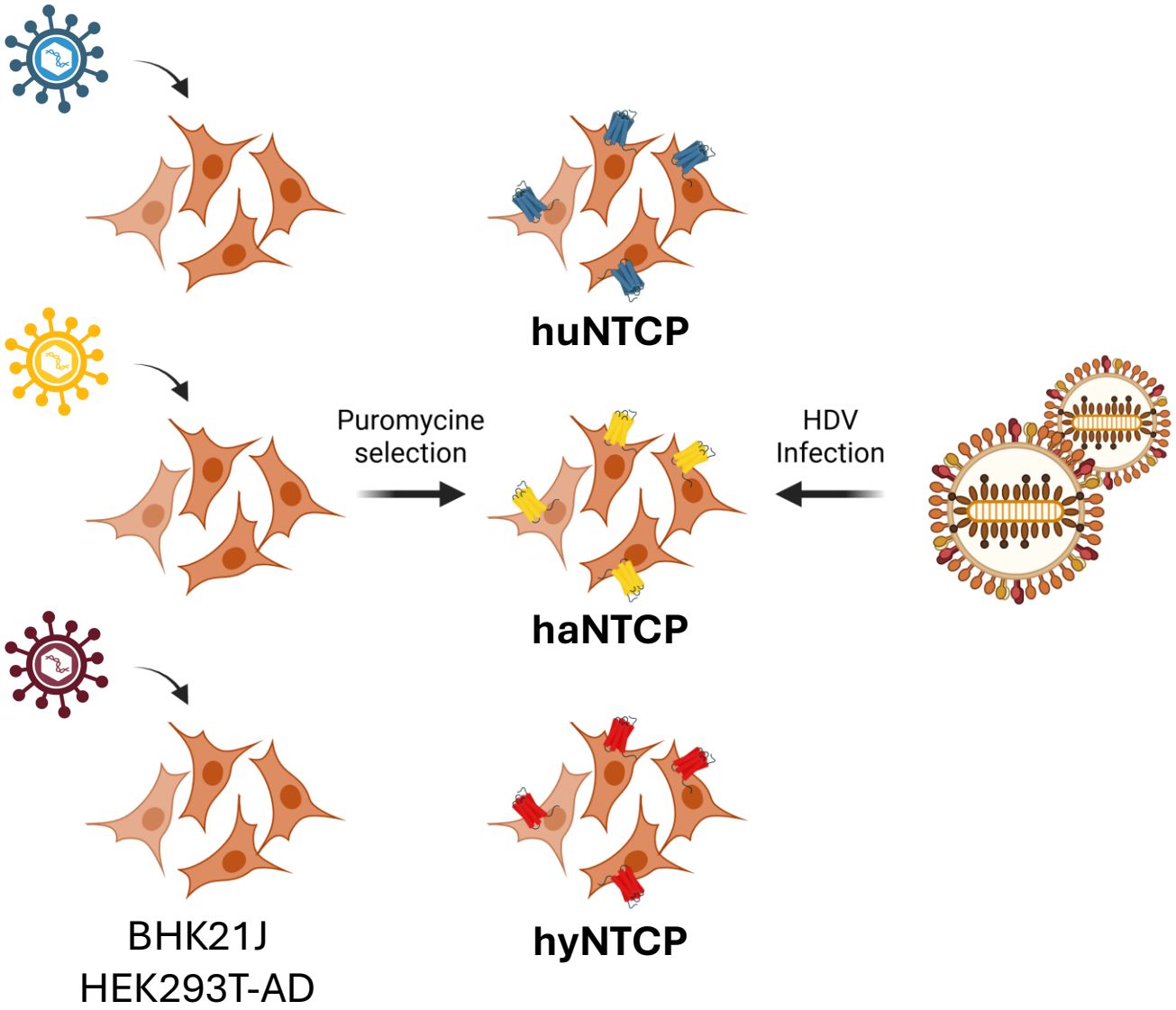
HDV Goes Hybrid

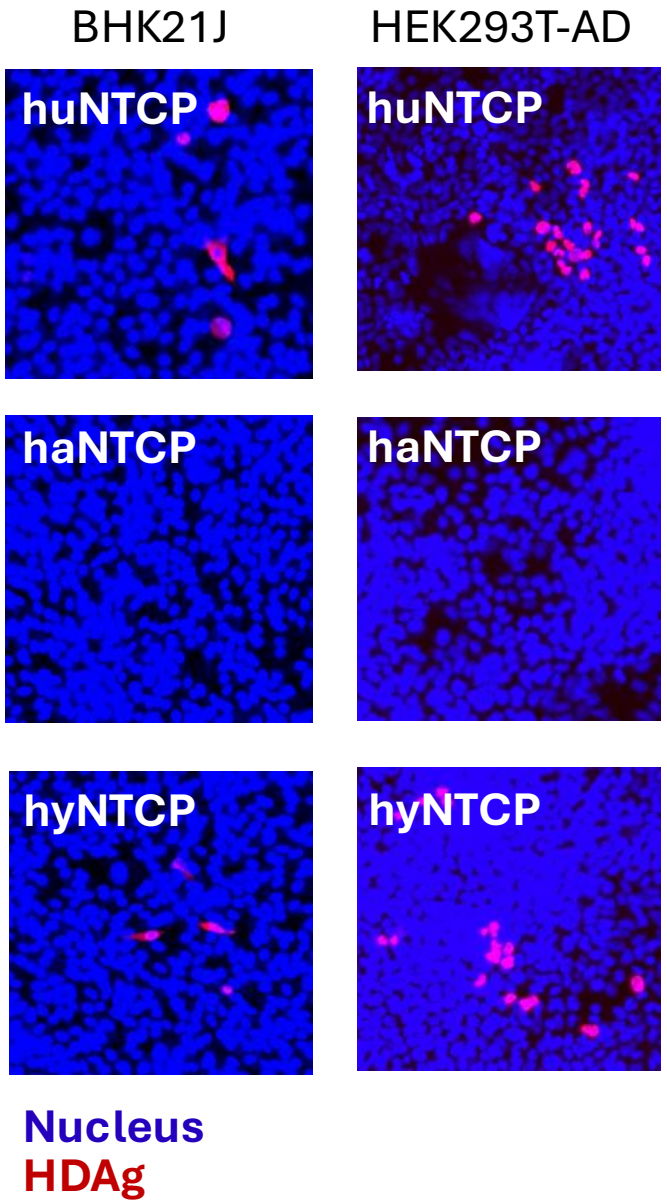


HDV Goes Hybrid

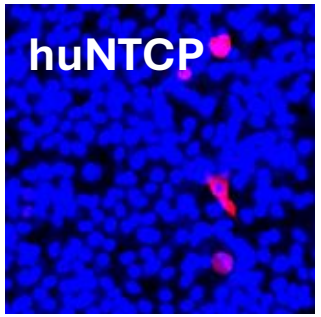


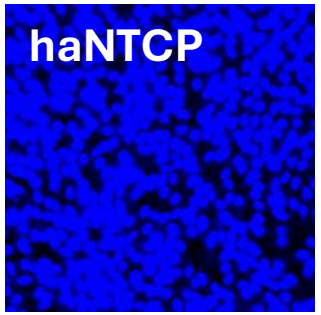
HDV Goes Hybrid

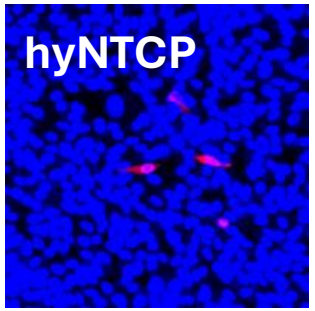




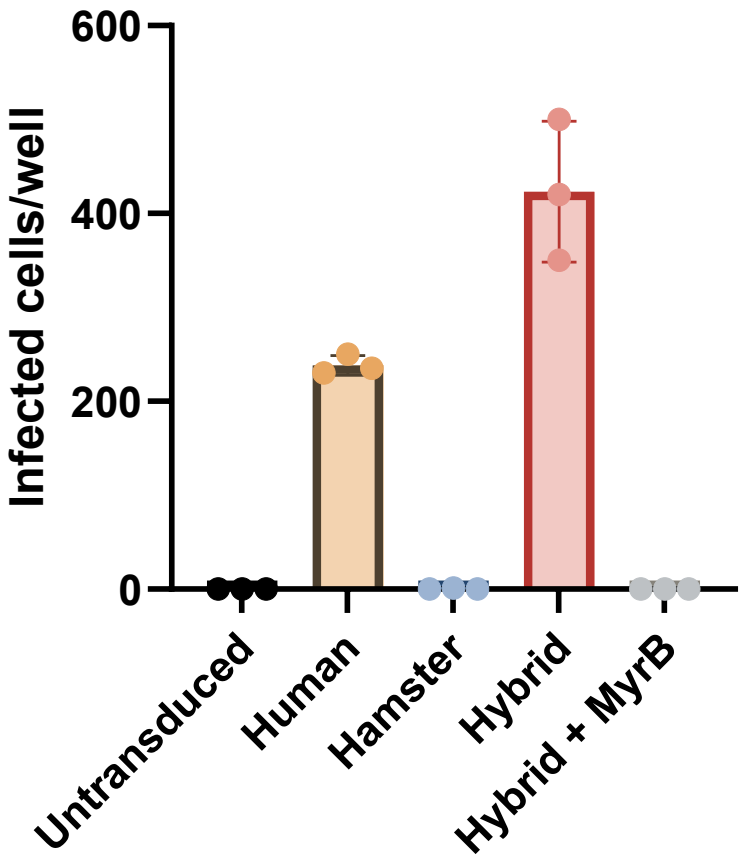
HDV Goes Hybrid

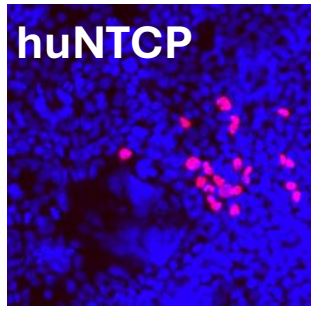


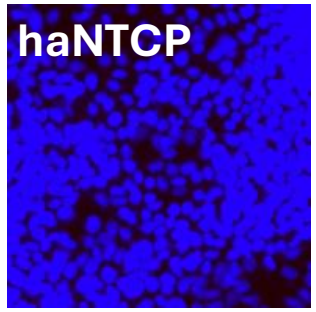


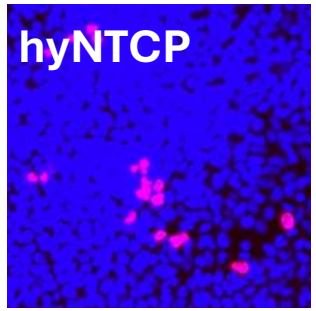


Nucleus
HDAg

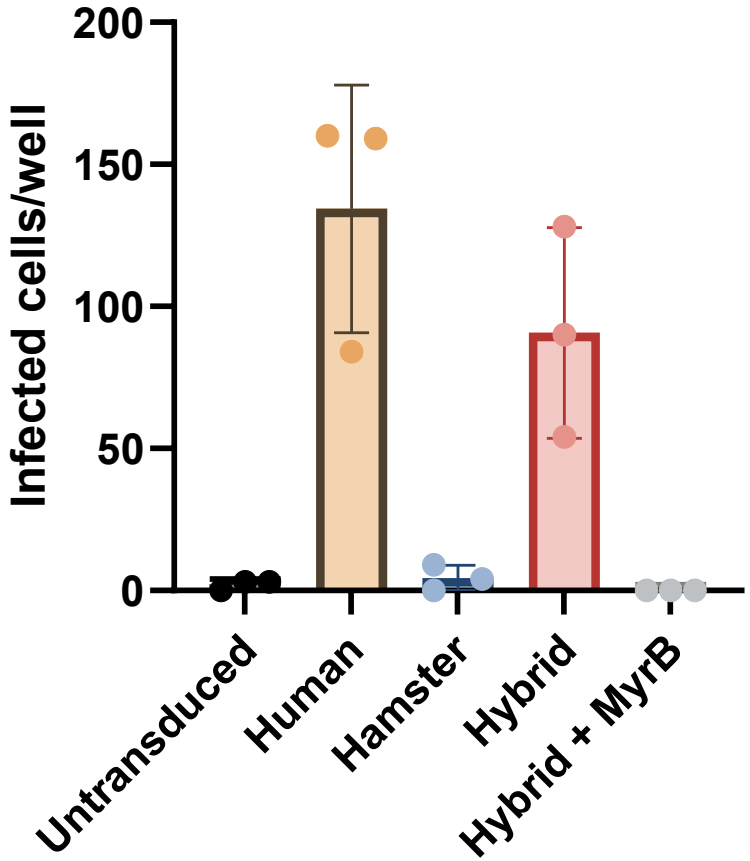




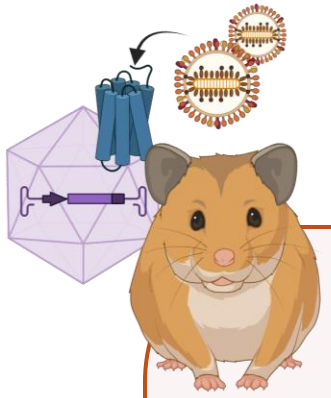




Nucleus
HDAg

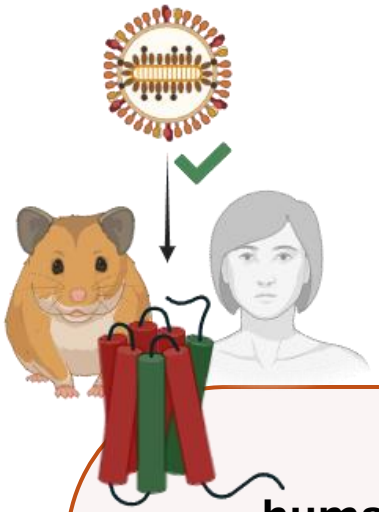


Conclusions



In vivo
hNTCP hamster model

- hNTCP rescues HDV susceptibility
- Long-term infection in an immunocompetent model
- Validated for antiviral testing
- Compound 116 + ritonavir combination therapy protects against HDV infection



In vitro
humanized hamster NTCP

- R→K — Humanizing only 3 amino acids renders hamster NTCP susceptible to HDV
- Hybrid NTCP as susceptible compared to human NTCP

Acknowledgements

Molecular Vaccinology & Vaccine Discovery
Prof. Kai Dallmeier
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Prof. Ir. Rik Gijsbers
Dr. Chris Van Den Haute
Maxime Smits

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Dr. Hendrik Jan Thibaut
Dr. Madina Rasulova

ALIGOS Therapeutics
Dr. Yannick Debing
Dr. Dave McGowan
Lars Degrauwe

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KU LEUVEN

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HBV INTERNATIONAL MEETING