# Role of HIV-1 Nef in Acceleration of HCV-Mediated Liver Disease

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# HIV-1/HCV co-infection

* Shared routes of infection:
    - sexual contact
    - blood stream
    - IDU

* Common with ~ 30% of all HIV-1-infected persons

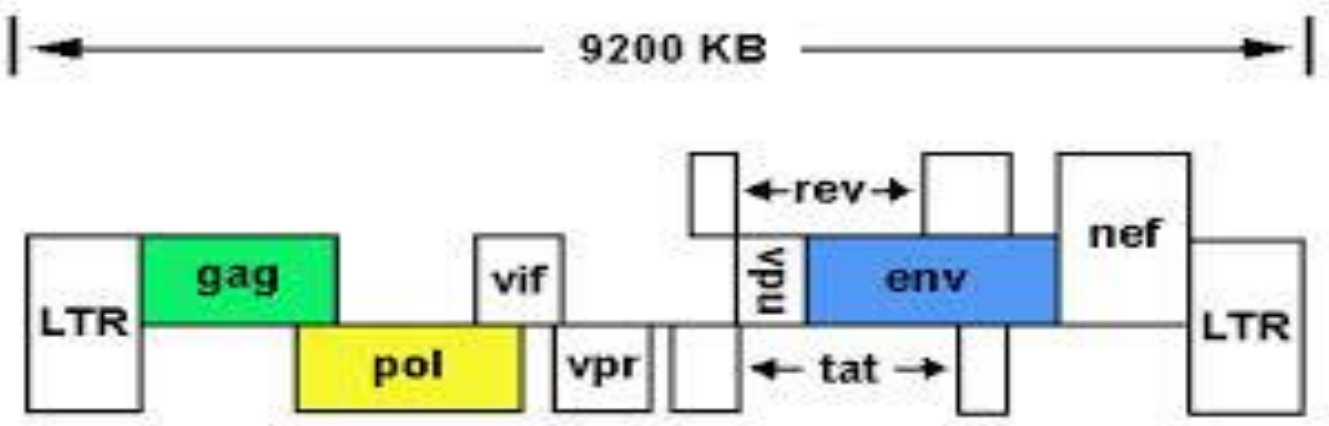
**Co-infection has profound, adverse consequences.**

**- elevate HCV viral load.**
**- expedite HCV-mediated liver disease progression.**

- **two-fold acceleration of fibrosis**
- **five-fold higher risk of cirrhosis-related liver complications, etc.**

- **Cirrhosis and end-stage liver disease – 50% of all deaths in co-infected patients - leading cause of morbidity and mortality in Western countries.**

# Genomic and virion structure of HIV-1

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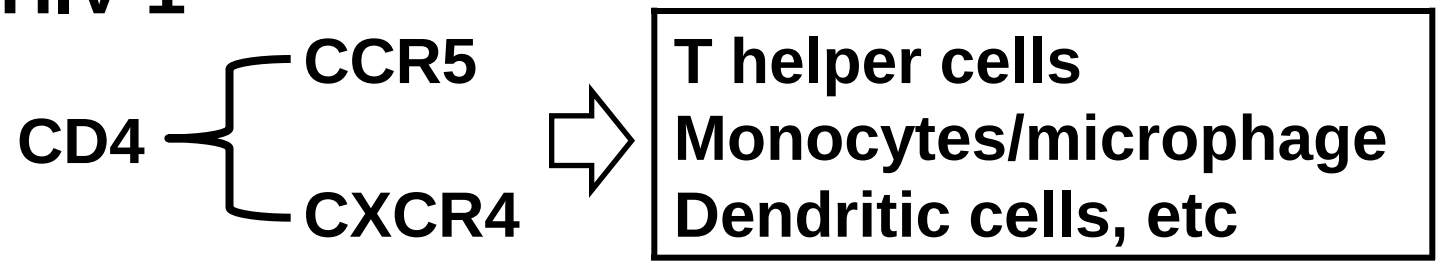
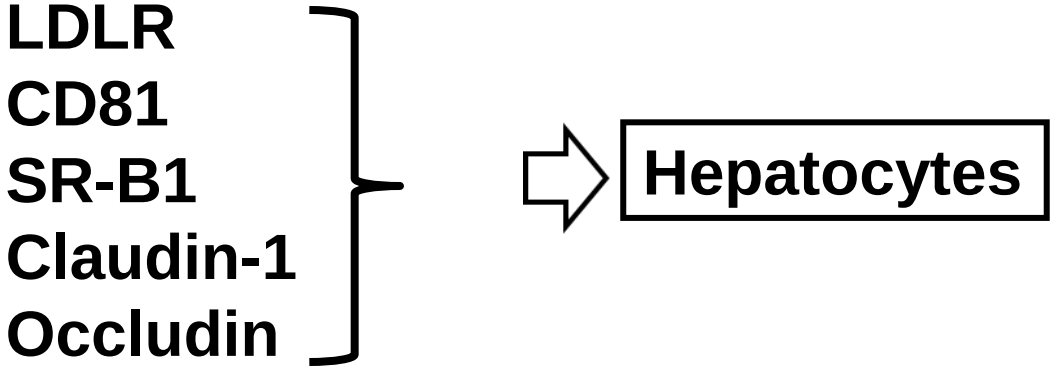
| | |
|---|---|
| **Structural:** | **Gag, Pol, and Env** |
| **Regulatory:** | |
| **Early:** | **Tat, Rev, and Nef** |
| **Late:** | **Vpr, Vpu, Vif** |

# Distinct target cells for infection

1. **Receptor/co-receptors**
   - A. **HIV-1**




   - B. **HCV**



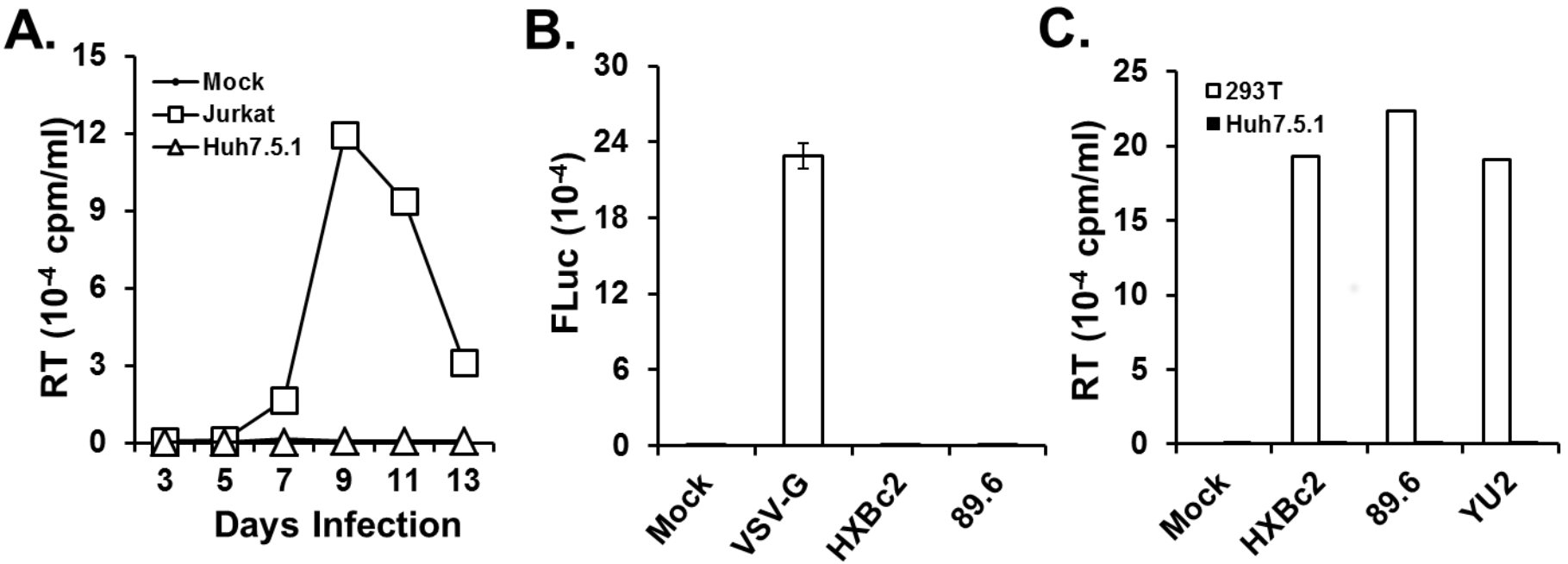

2. **Fundamentally different life cycles**

# Possible mechanisms

1. **Direct infection of HIV-1 into HCV-infected hepatocytes/HSC**

2. **Indirect effect**
   - **A. Viral proteins, such as Env, Tat, and Nef**
   - **B. Dysfunction immune systems by HIV-1 and/or viral proteins**

# Replication of HIV-1 in human hepatocytes



# Viral protein candidates

1. **Env - interact with CXCR4 or CCR5 co-receptor**
   - ➡ **enhance HCV replication in the replicon**
   - ➡ **induce apoptosis**

2. **Tat - diffusible protein**
   - ➡ **enhance hepatocarcinogenesis in transgenic mice**

# Relevant Nef functions for up-regulation of HCV replication

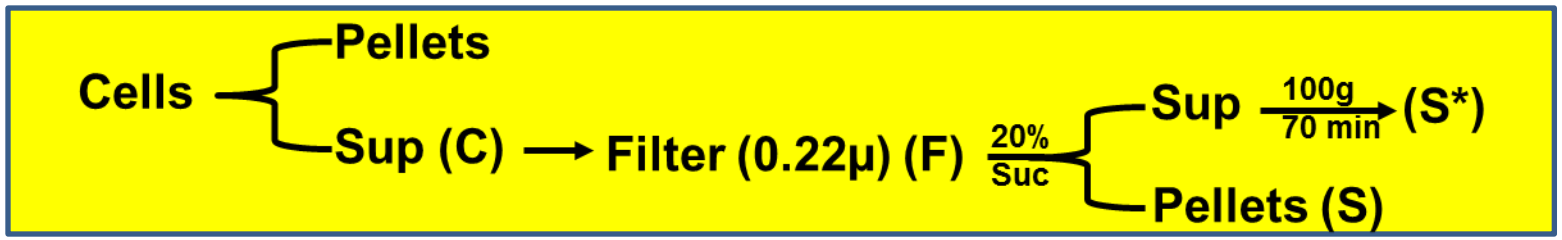
1. **Induces formation of conduits (filopodia) and secretion of exosomes.**

2. **Regulates the amount of intracellular lipids by modulating expression of lipid molecules.**

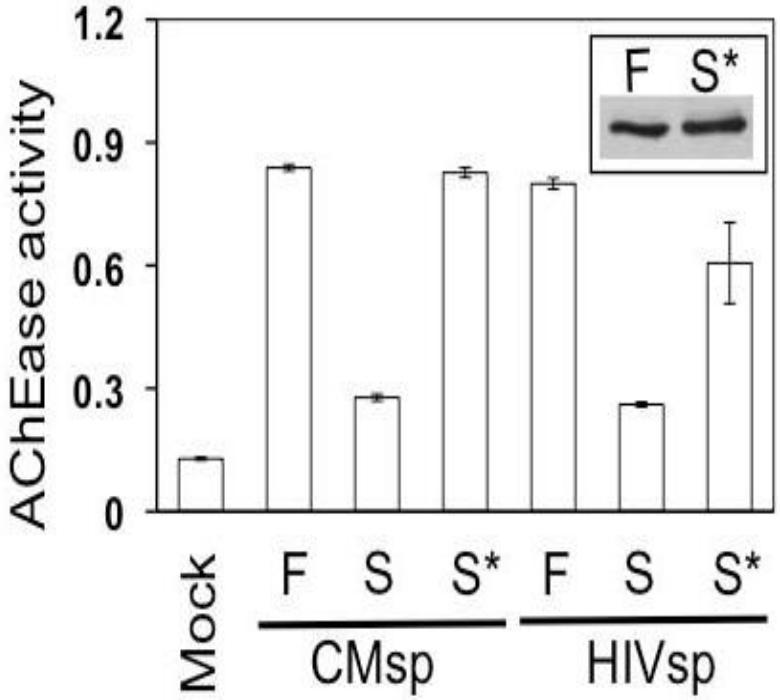
3. **Forms complexes with and thereby activates several cellular kinases, such as the Src family of tyrosine kinases.**

4. **Alters host immune responses.**

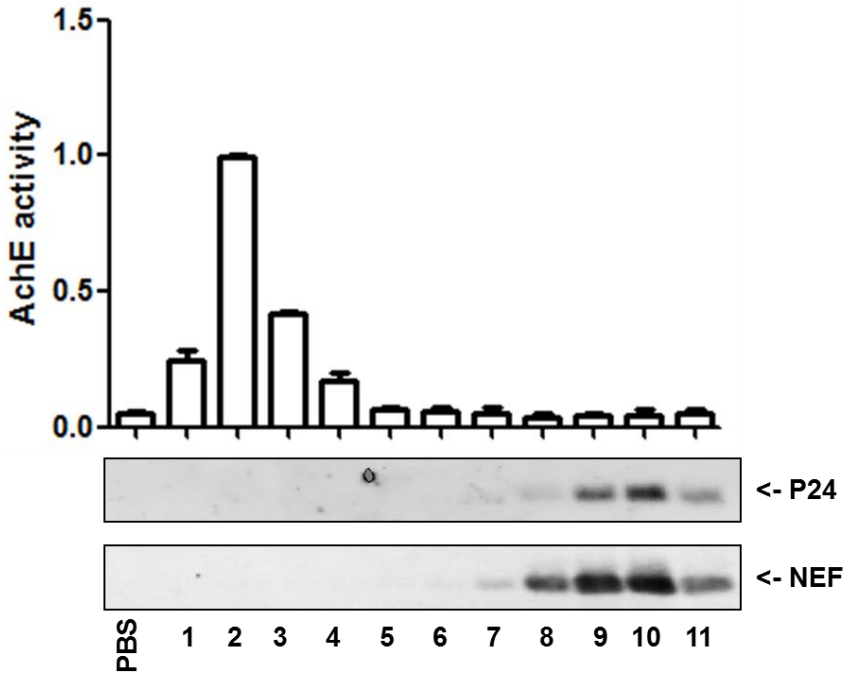
# Exosome-mediated Nef transfer?




**A.**

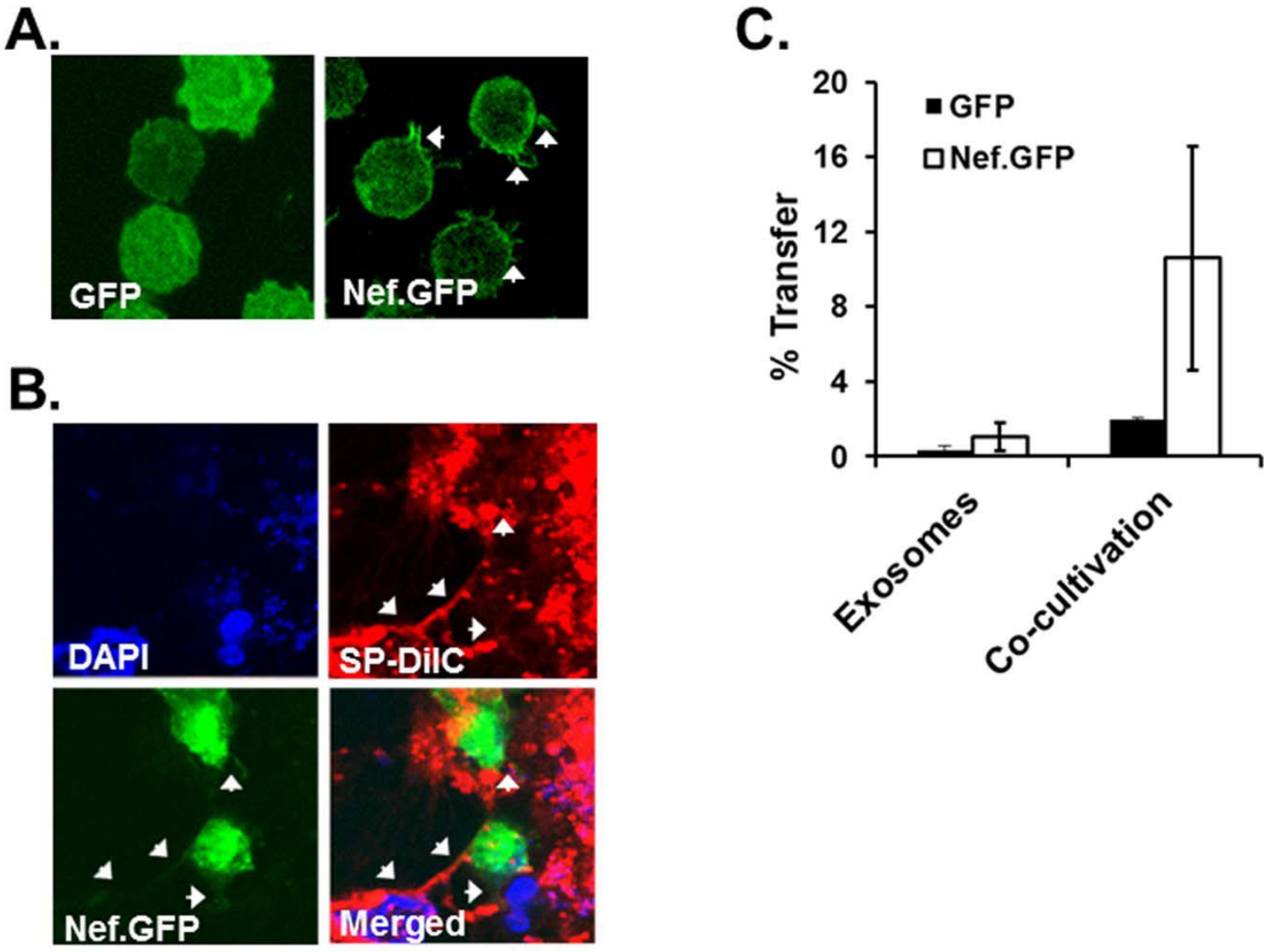



**B.**

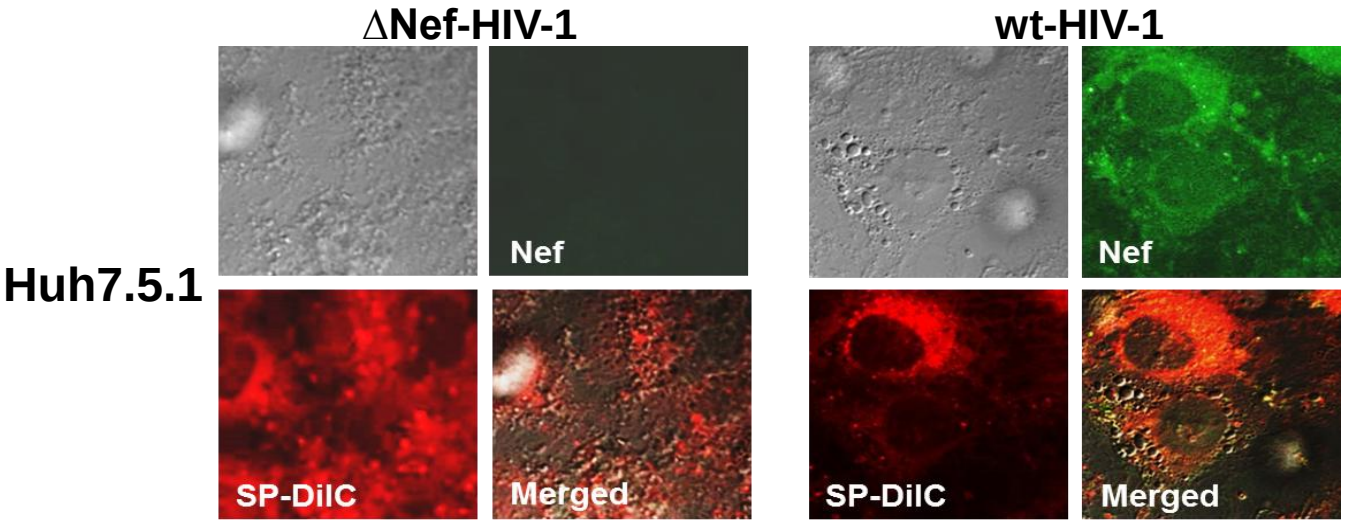



**Virol. J. 2011**

# Transfer of Nef protein from Jurkat T cells into hepatocytes.



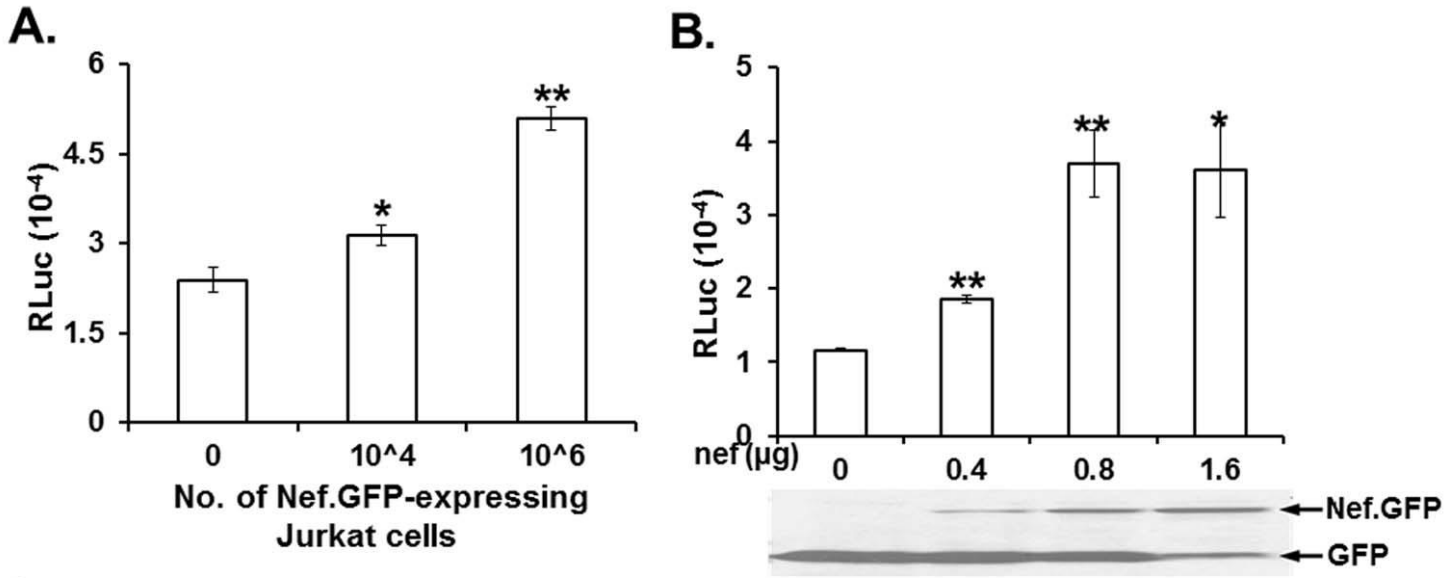
# Nef is transferred from HIV-1-infected cells to hepatocytes

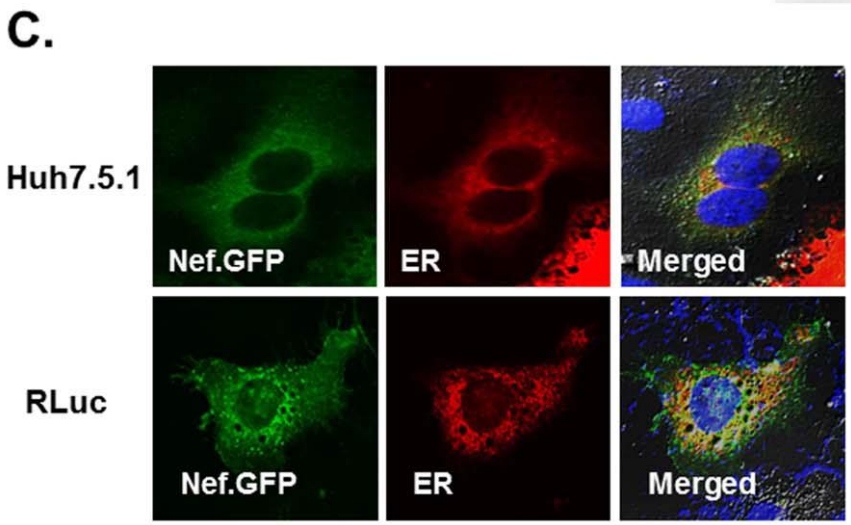


# Biological significance of Nef transfer

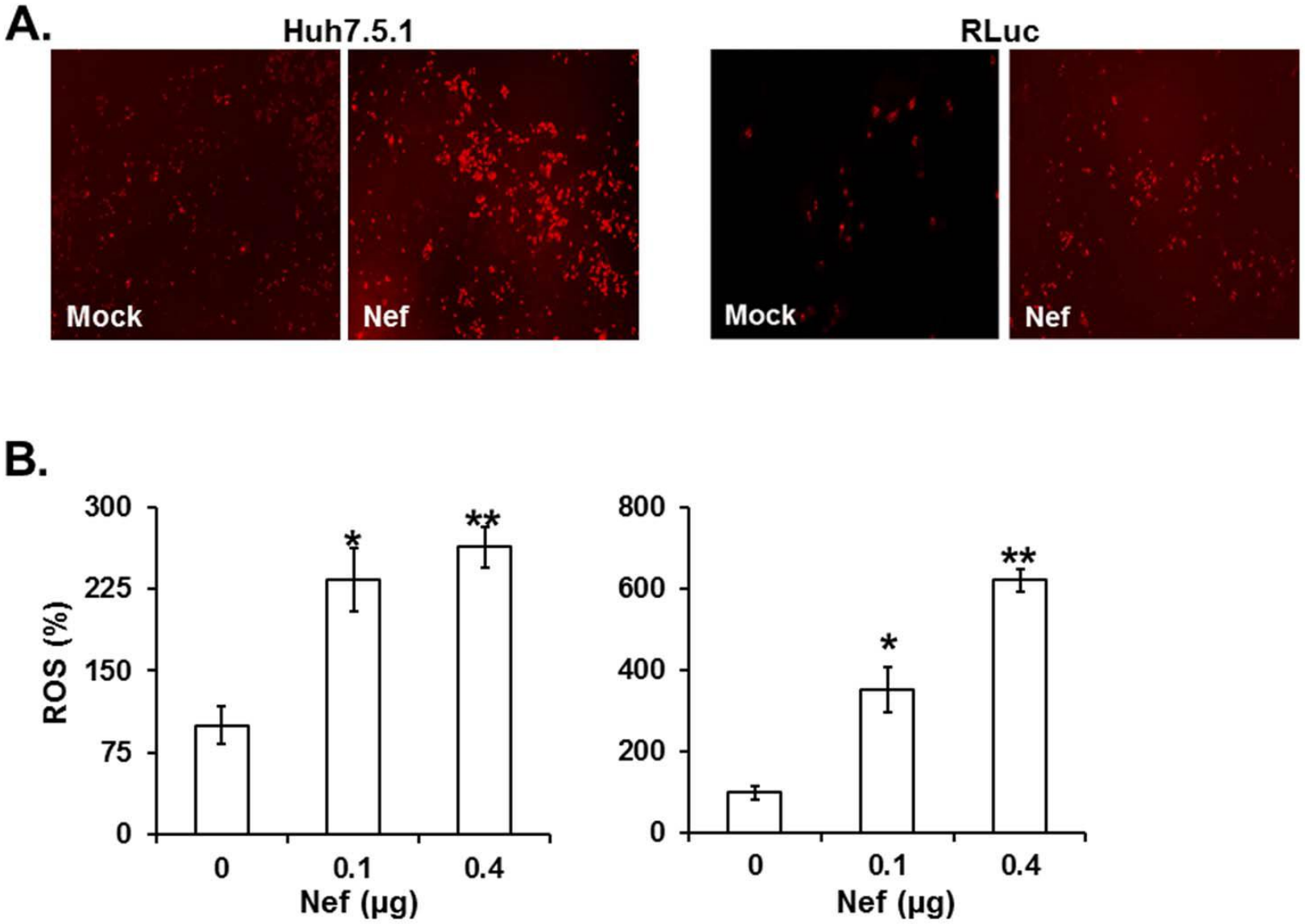
1. Up-regulation of HCV replication
2. Generation of ROS
3. Effect on alcohol-mediated up-regulation of HCV replication
4. Others

# Nef up-regulates HCV subgenomic replicon expression

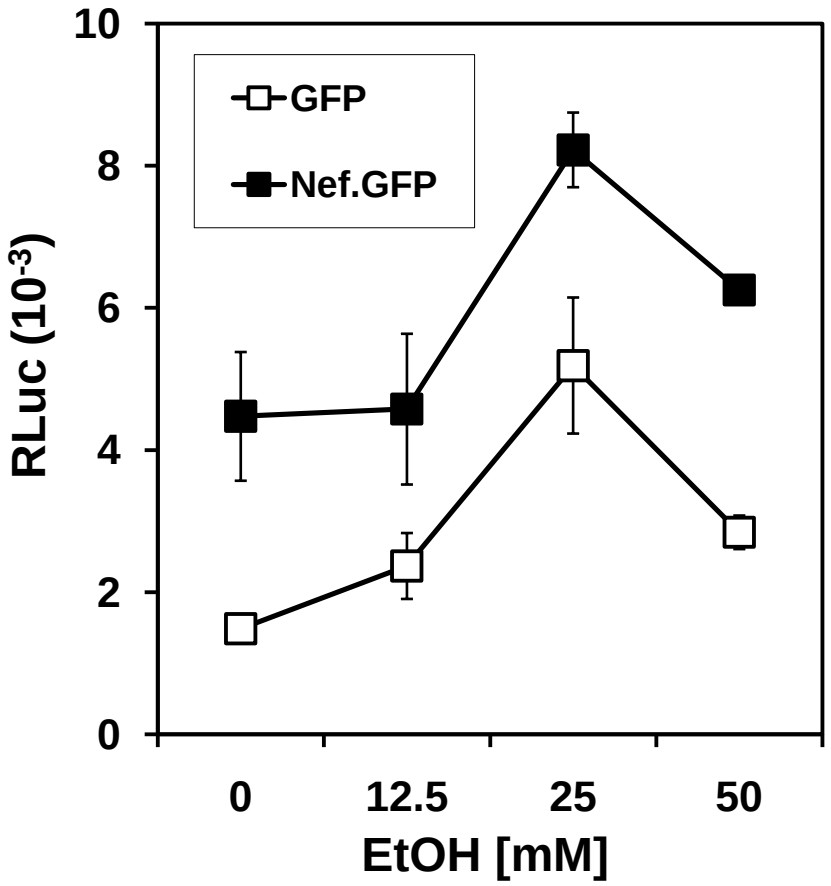


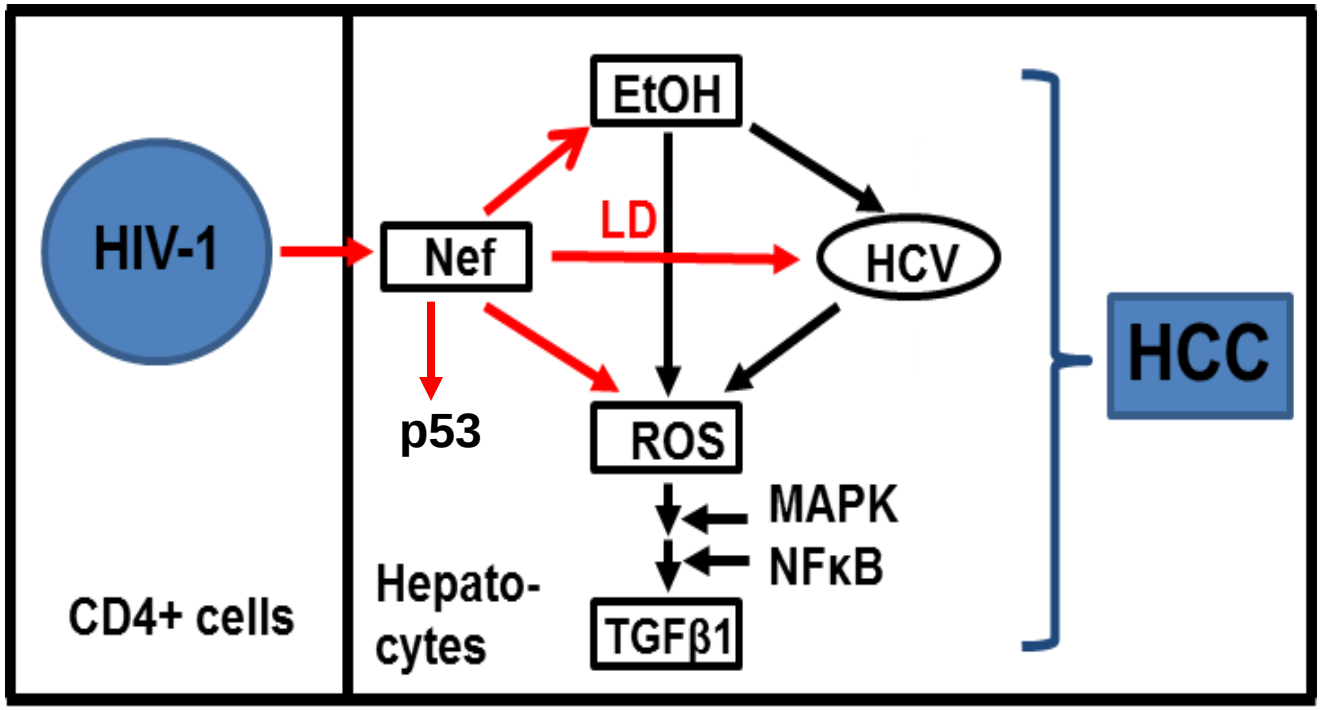
# Nef-mediated induction of ROS



# Effect of Nef on ethanol-mediated up-regulation of HCV replication



# Summary


HIV-1
CD4+ cells
Nef
p53
EtOH
LD
HCV
ROS
MAPK
NFκB
Hepato-
cytes
TGFβ1
HCC

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