

***mTOR inhibitors lower an intrinsic barrier to virus infection mediated by IFITM3***

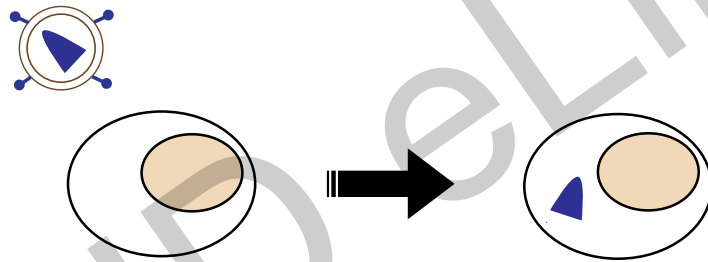
**Alex Compton, PhD**  
***HIV Dynamics and Replication Program***  
***National Cancer Institute***  
***Frederick, MD USA***



**NATIONAL  
CANCER  
INSTITUTE**

**ECCMID, April 14th 2019**

# Viruses enter cells in order to initiate infection



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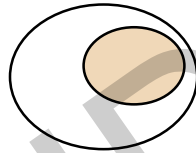
# Cell-intrinsic immunity: the first line of antiviral defense



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# Cell-intrinsic immunity: the first line of antiviral defense

ZIKV  
IAV  
HIV



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# Cell-intrinsic immunity: the first line of antiviral defense

## Intrinsic immune barriers acting at virus entry

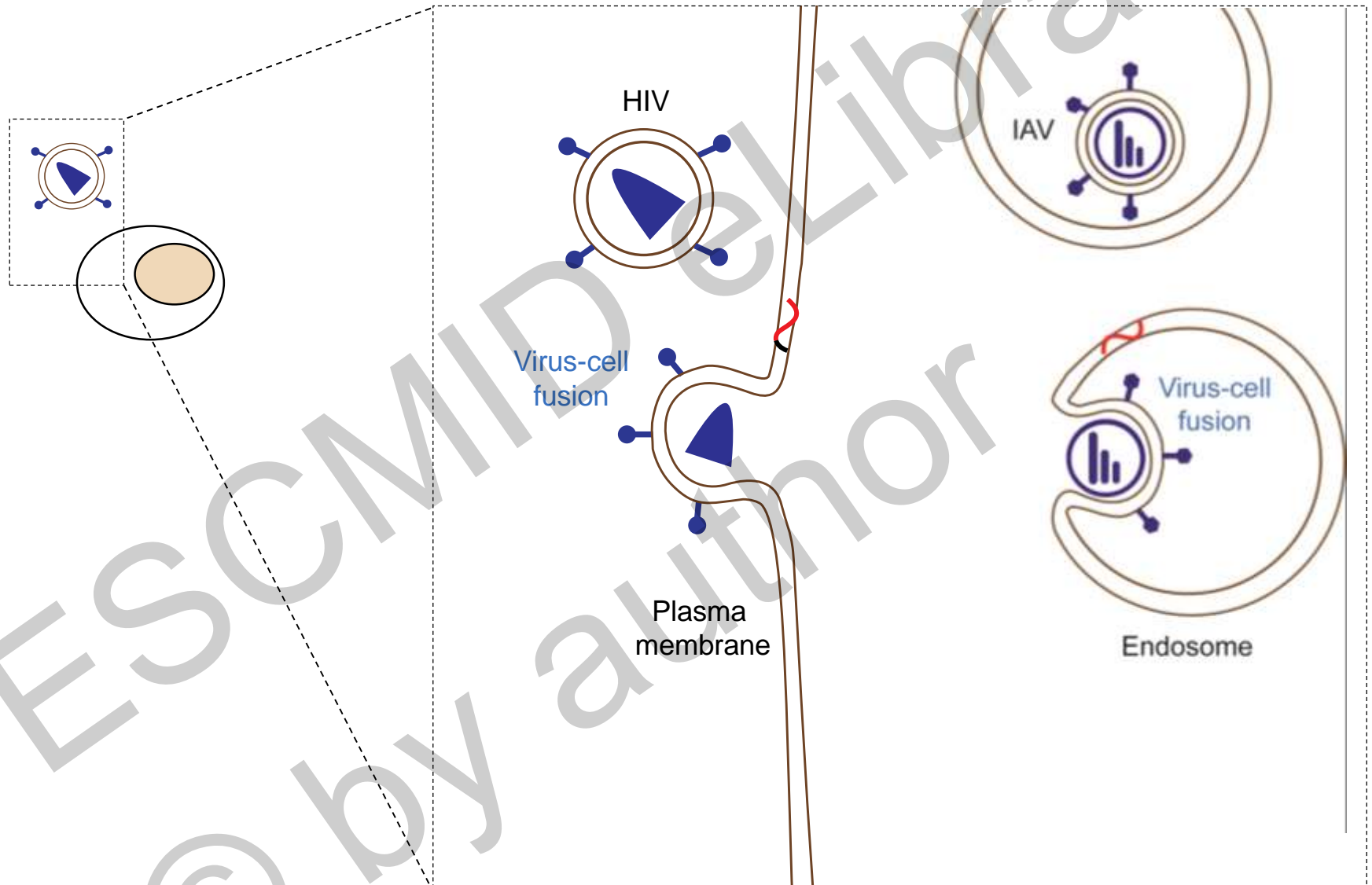
Mechanisms of virus entry  
restriction

Viruses as human  
pathogens

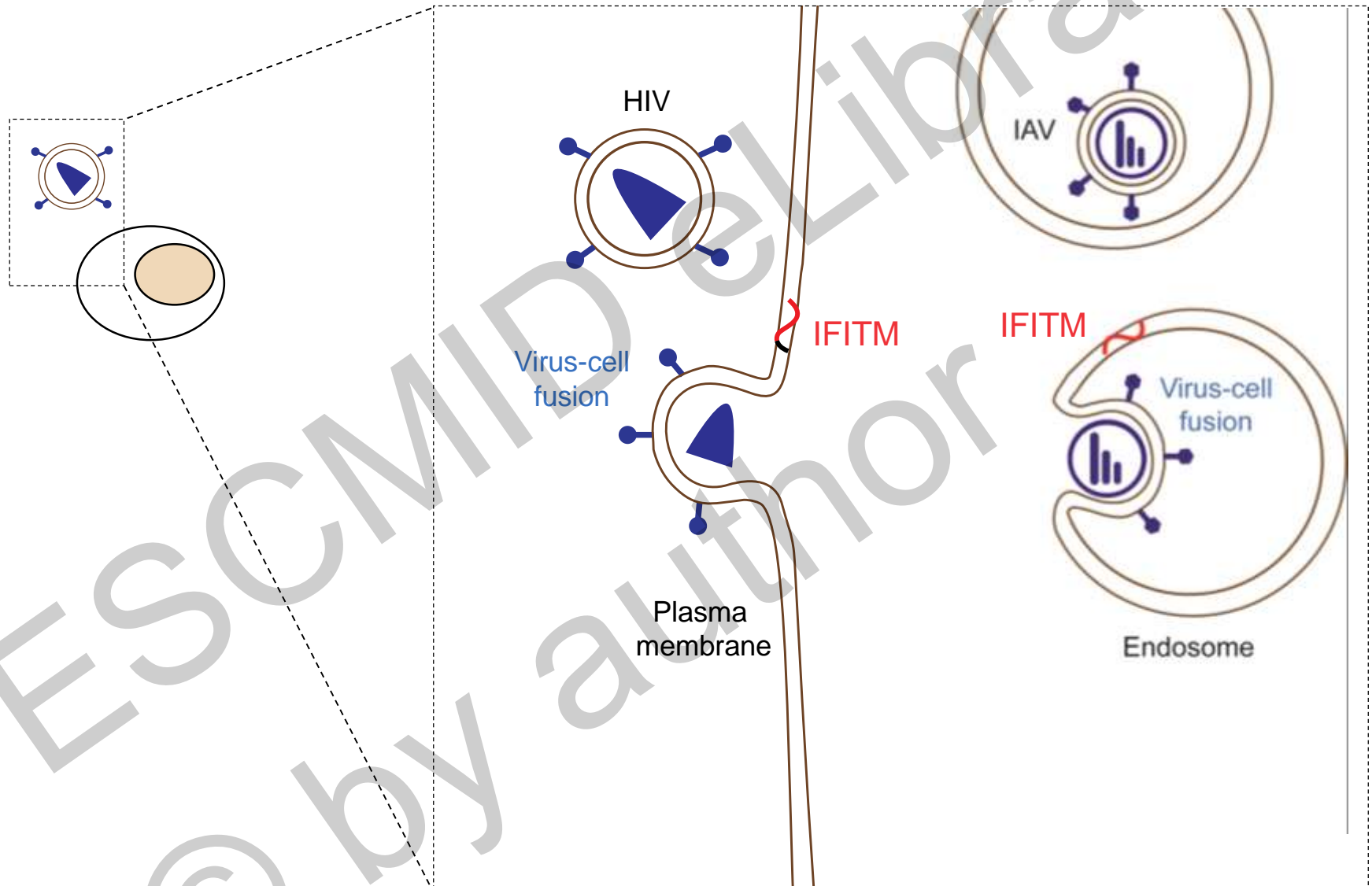
Mechanisms of virus entry  
enhancement

Viruses as tools for  
human innovation

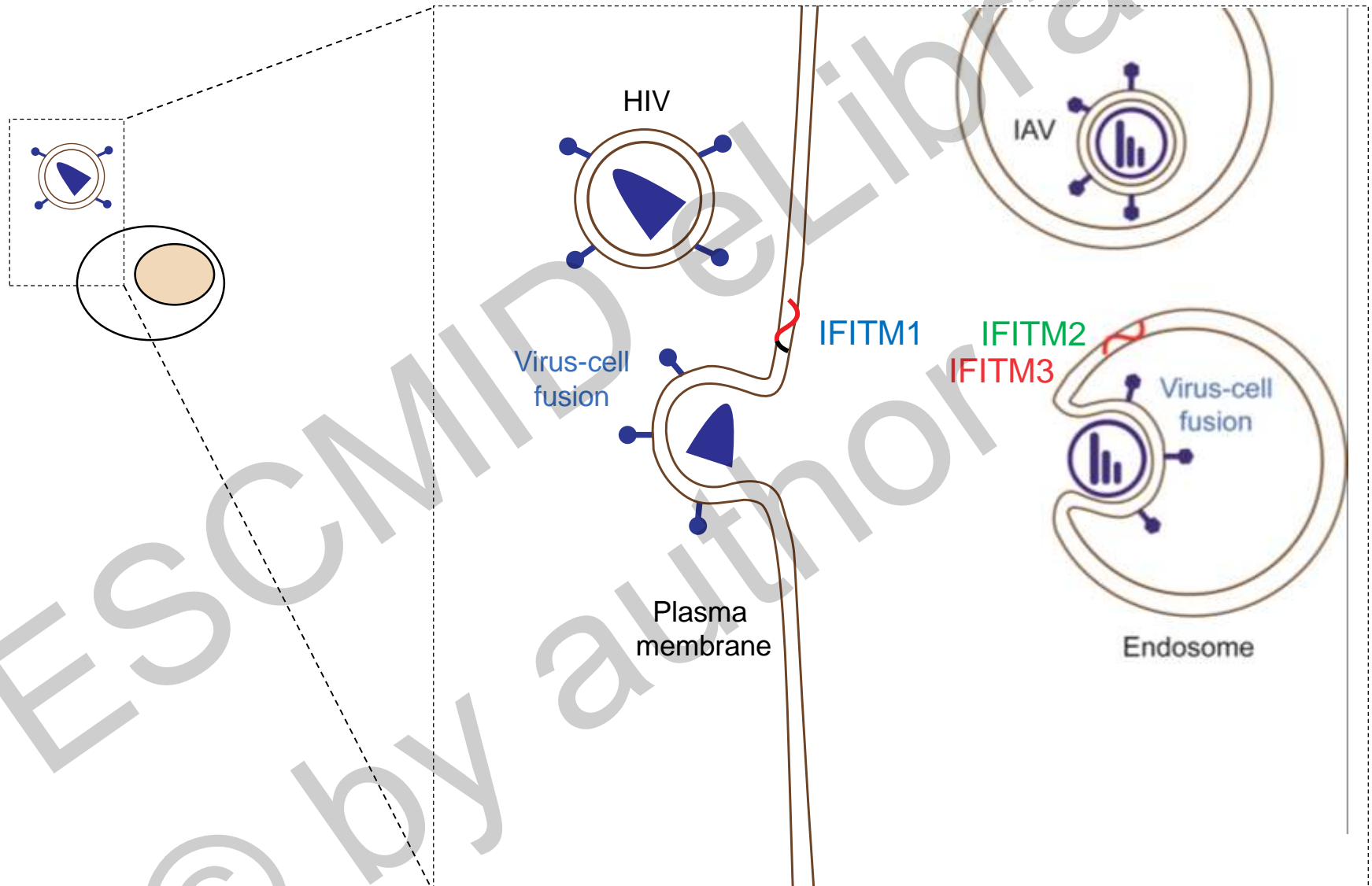
# Virus-cell membrane fusion: a crucial step towards infection



# IFITM proteins restrict virus entry by inhibiting virus-cell fusion

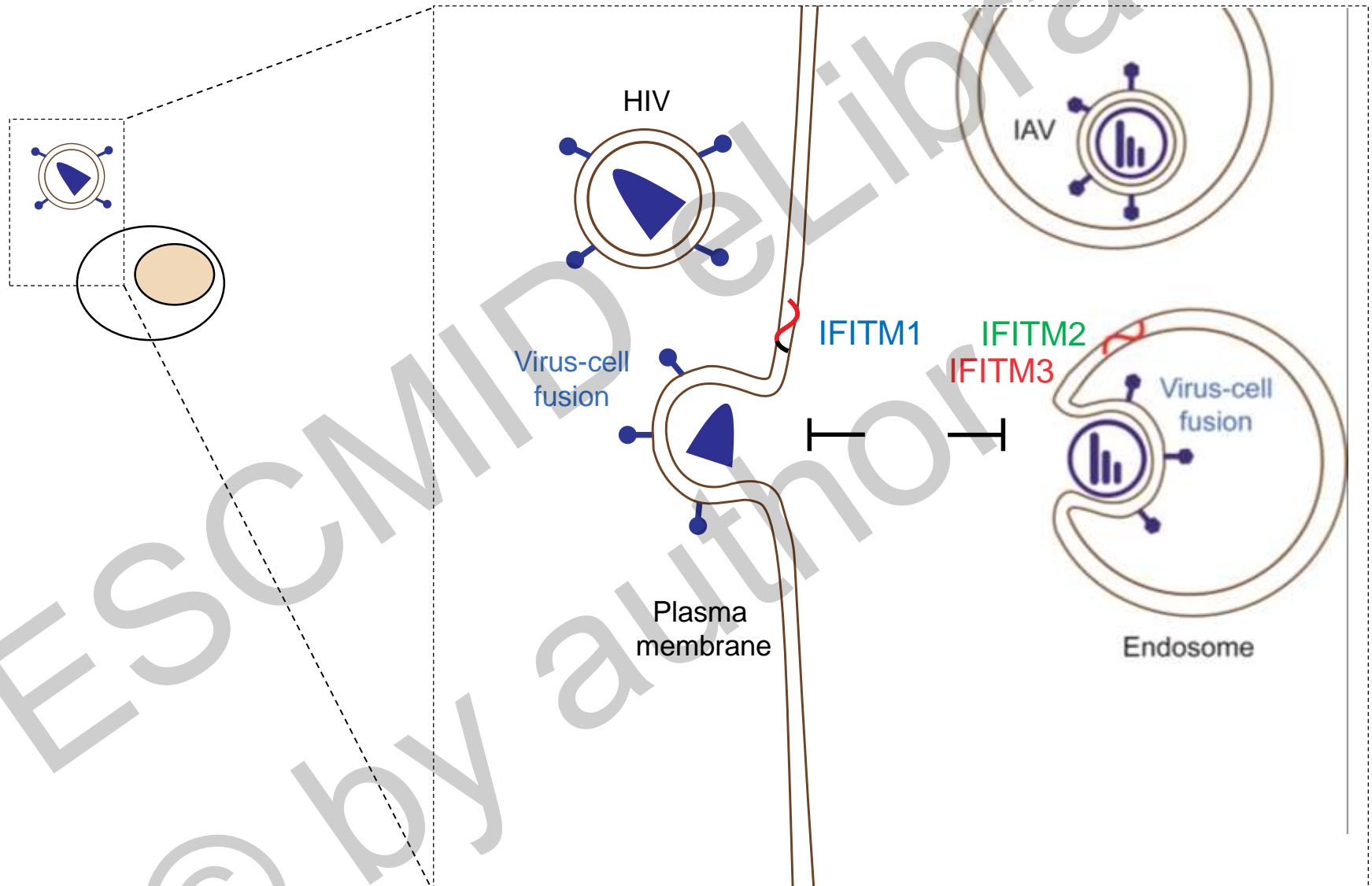


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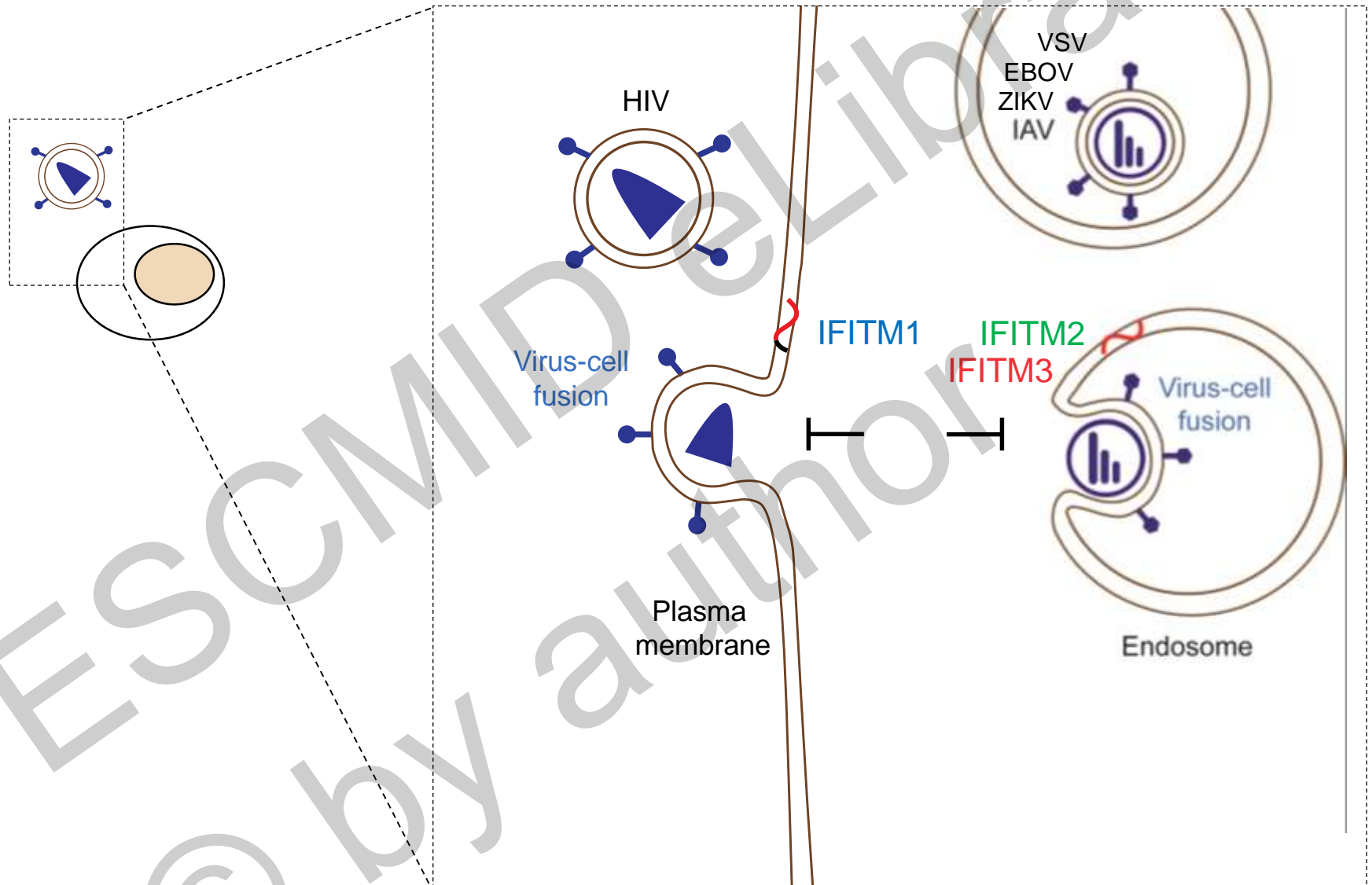




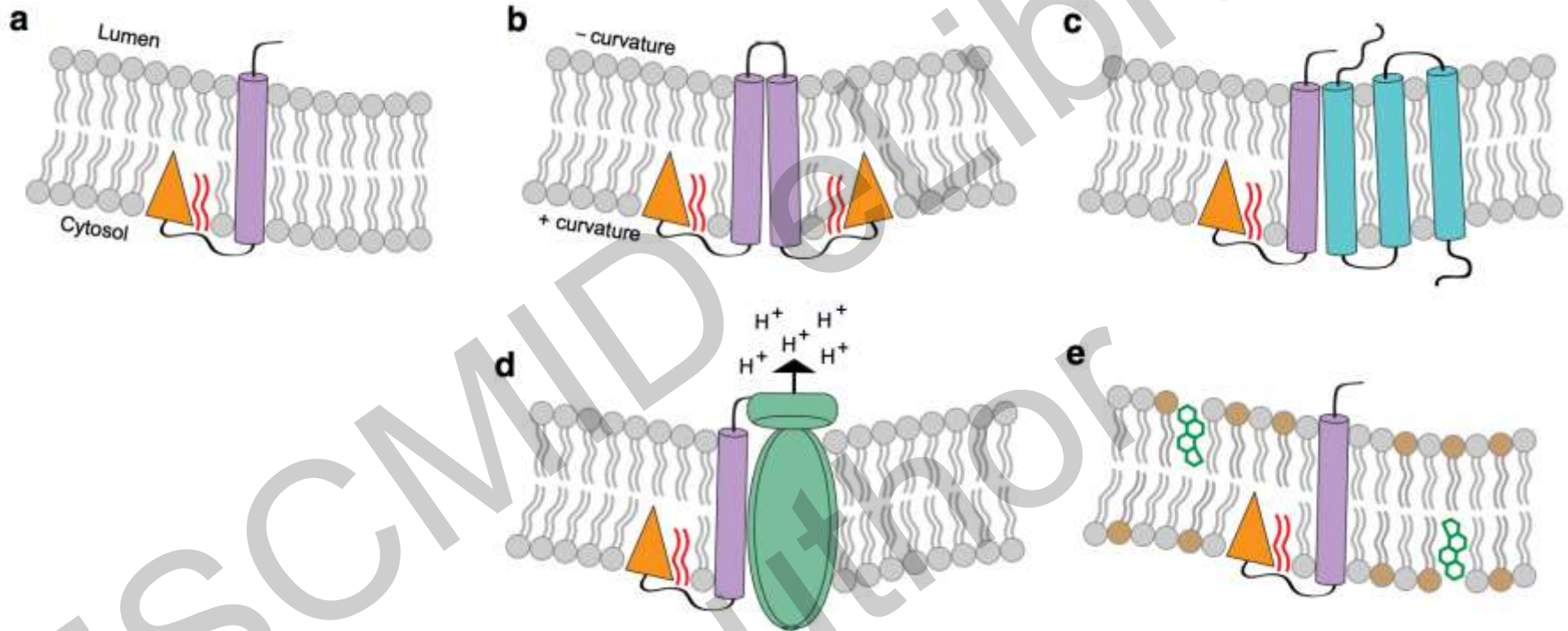
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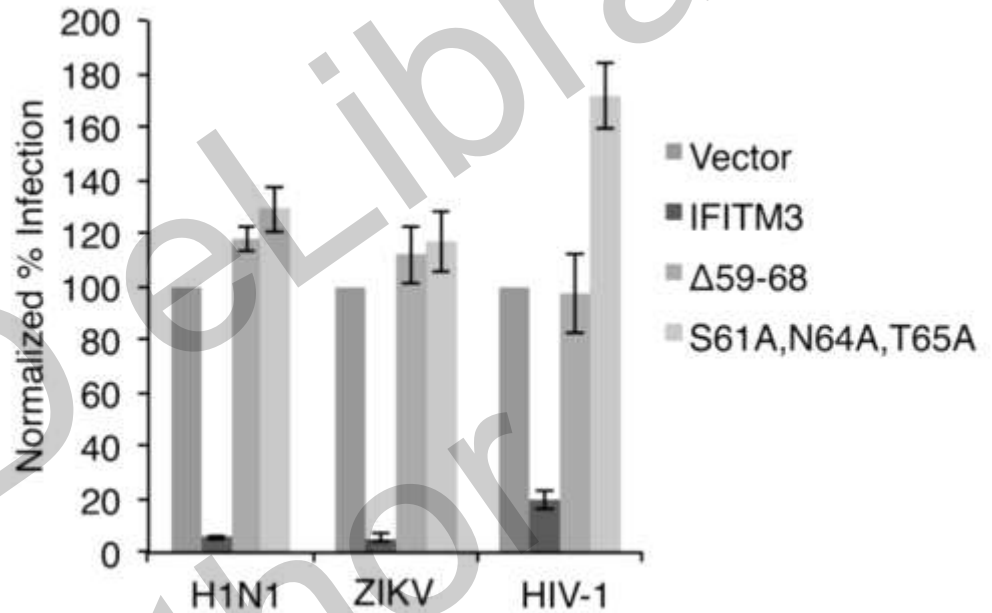
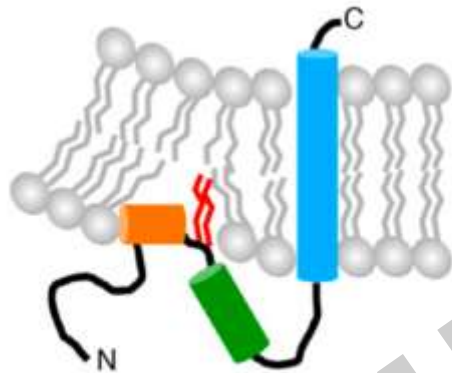
# IFITM proteins restrict virus entry by inhibiting virus-cell fusion



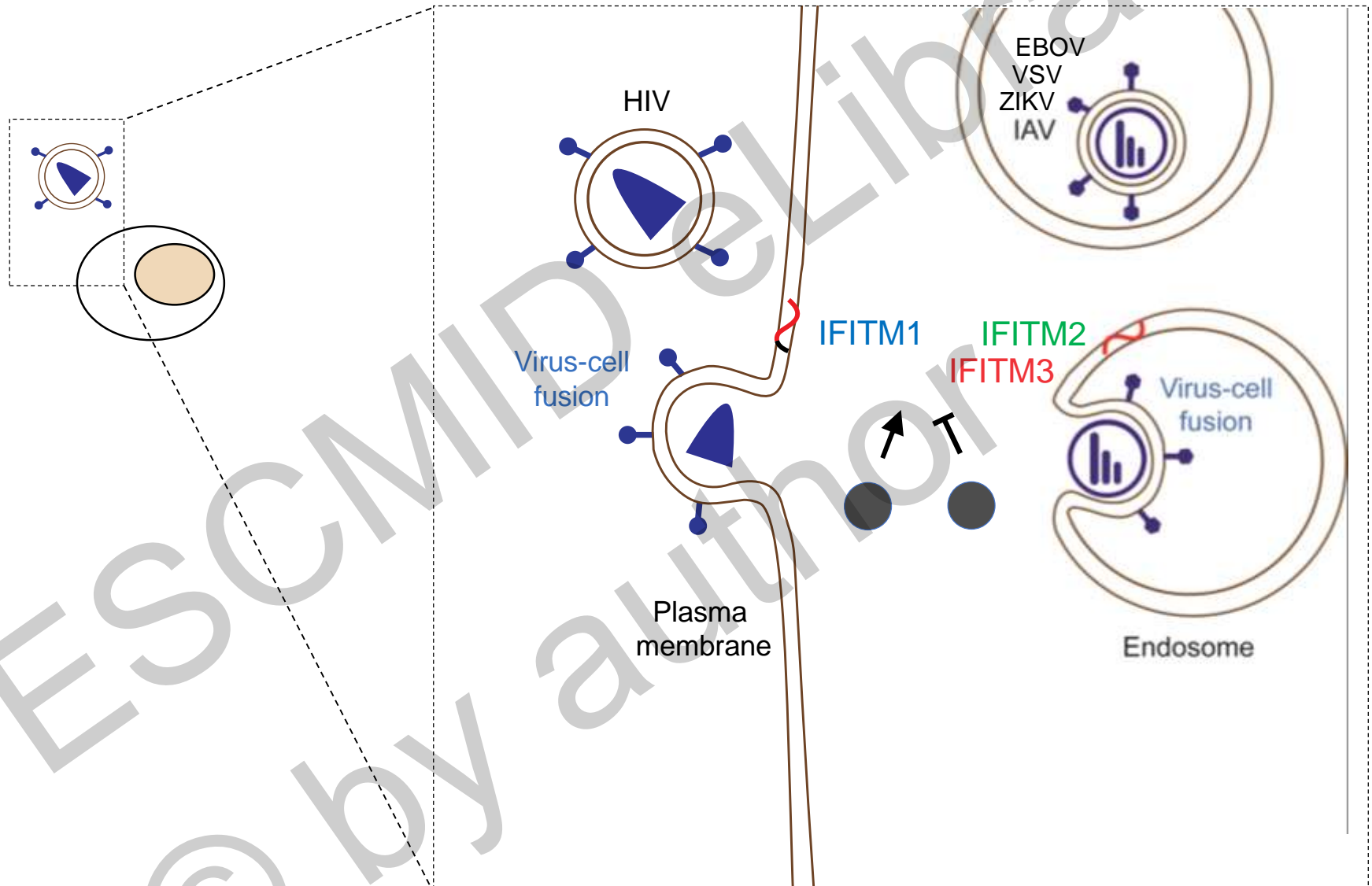
# IFITM3 is a membrane remodeling protein



# IFITM3 is a type II integral membrane protein



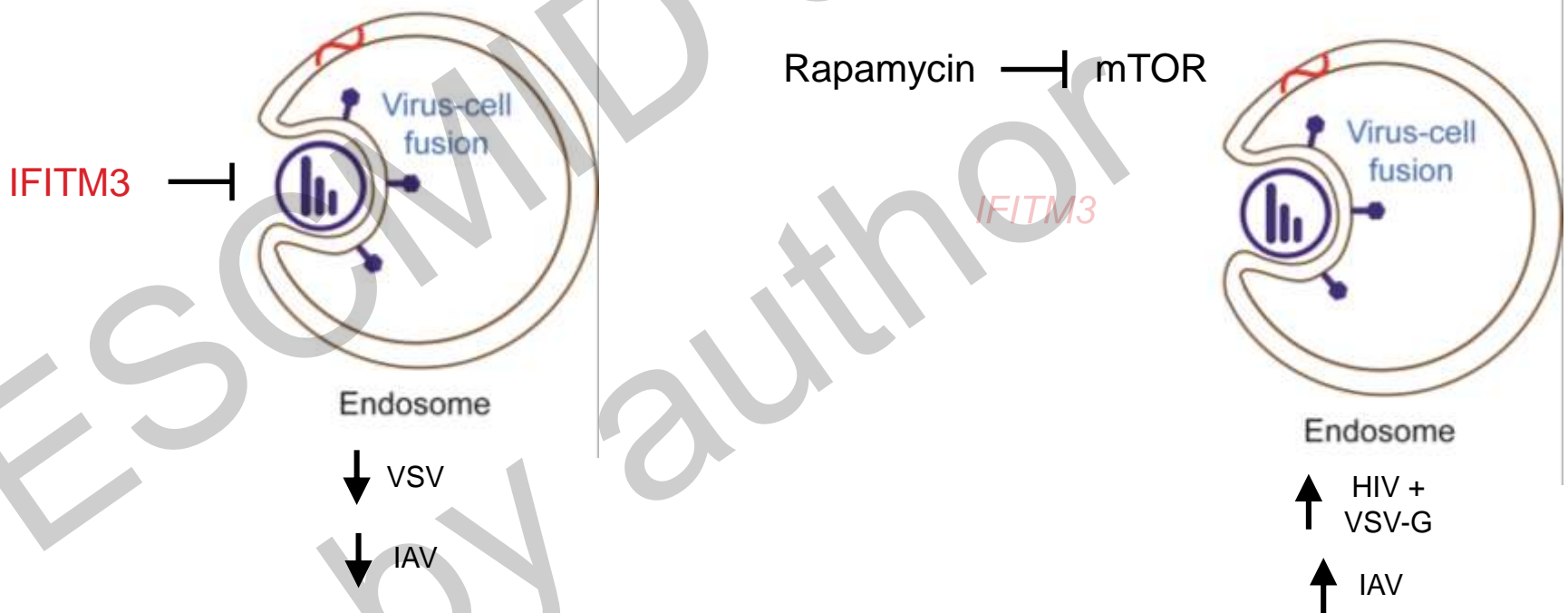
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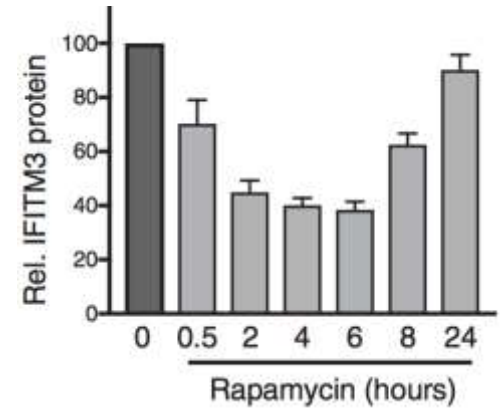
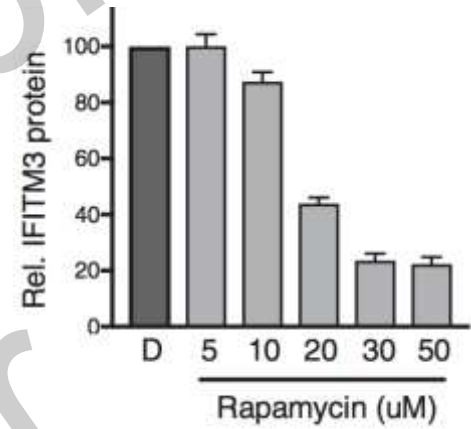
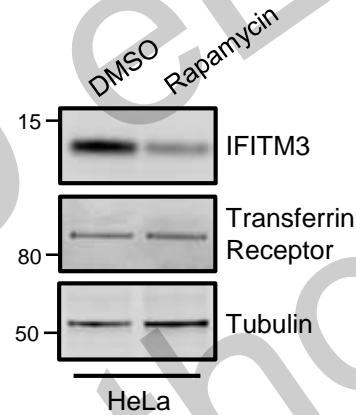
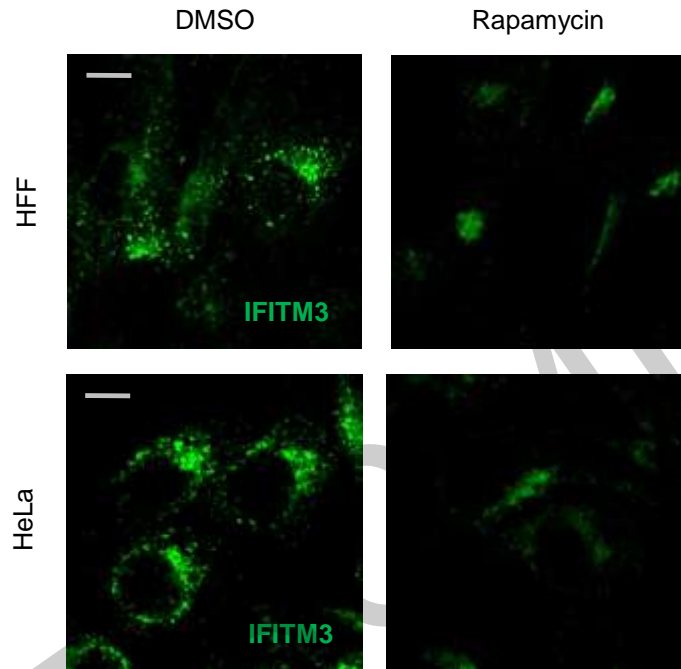
# The mTOR pathway as novel regulator of IFITM3

## mTOR inhibitors lower an intrinsic barrier to virus infection mediated by IFITM3

Guoli Shi<sup>a</sup>, Stosh Ozog<sup>b</sup>, Bruce E. Torbett<sup>b</sup>, and Alex A. Compton<sup>a,1</sup>

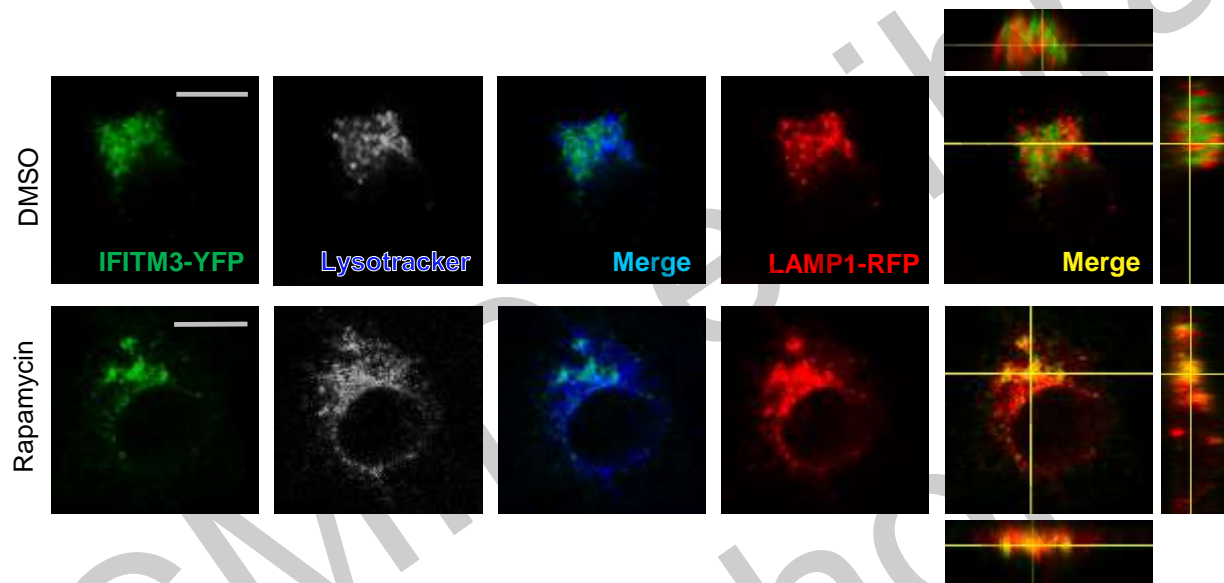


# mTOR inhibitor Rapamycin negatively regulates IFITM3





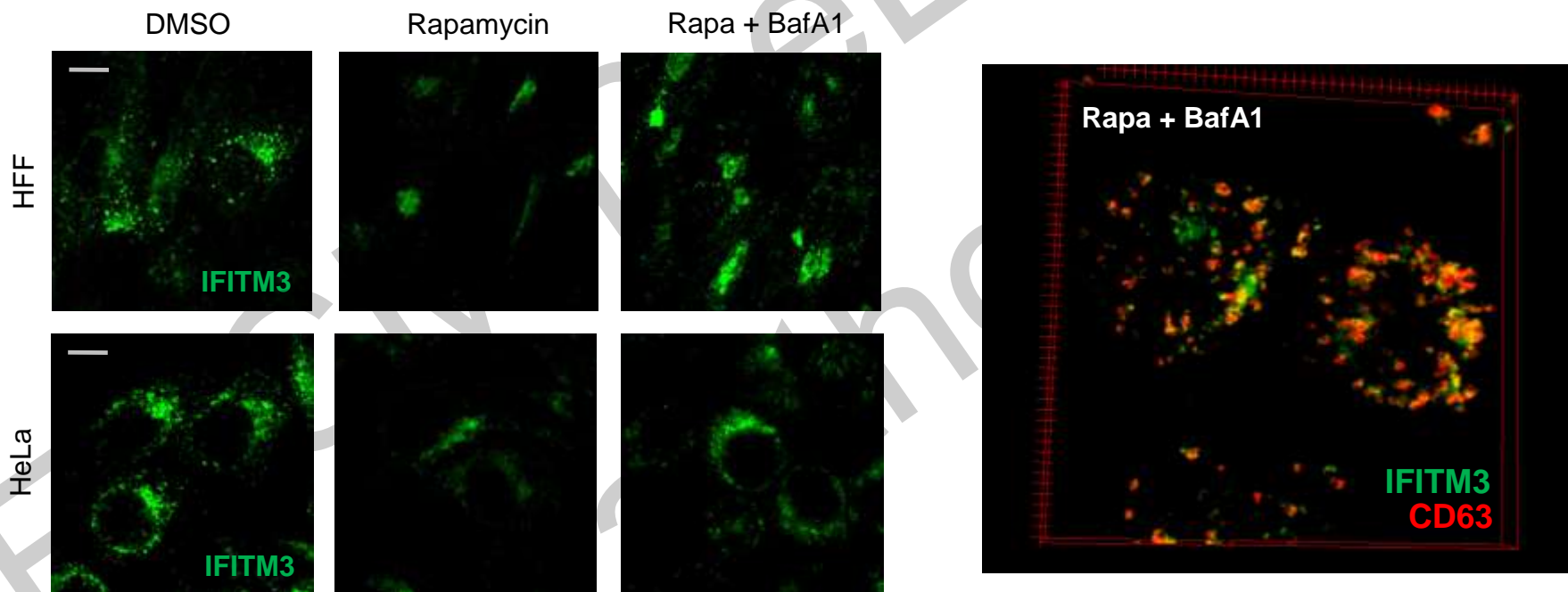
# Rapamycin leads to IFITM3 degradation in lysosomes...



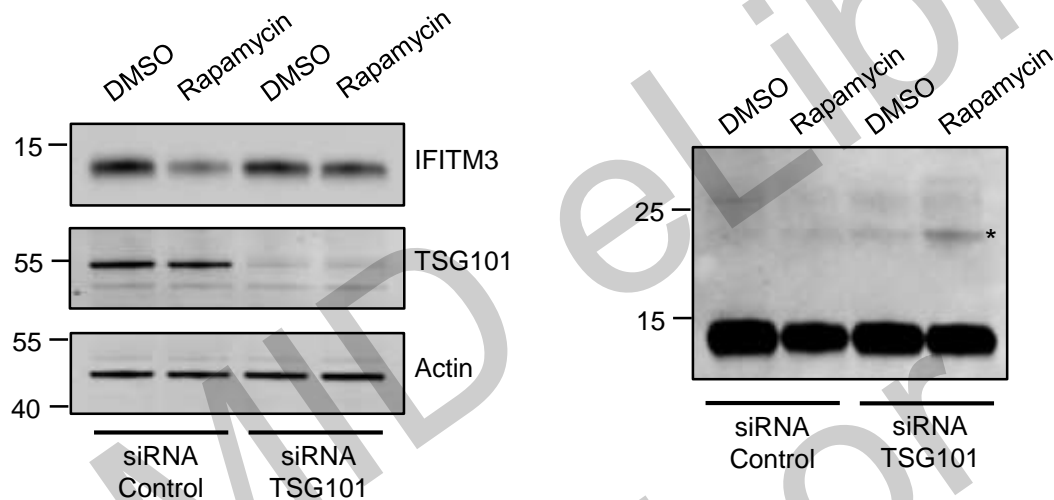


Rapamycin leads to IFITM3 degradation in lysosomes...

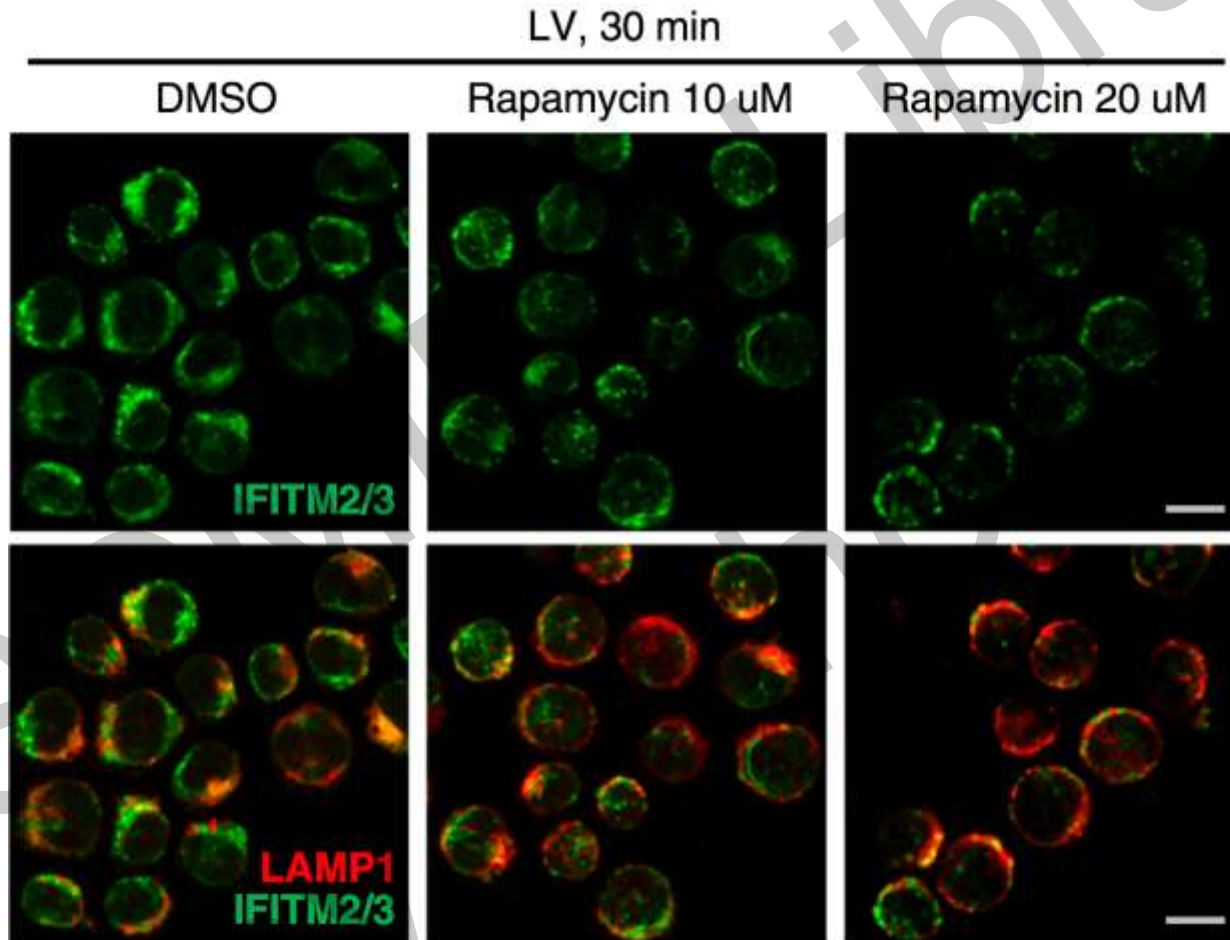
...following trafficking through multivesicular bodies (MVB)



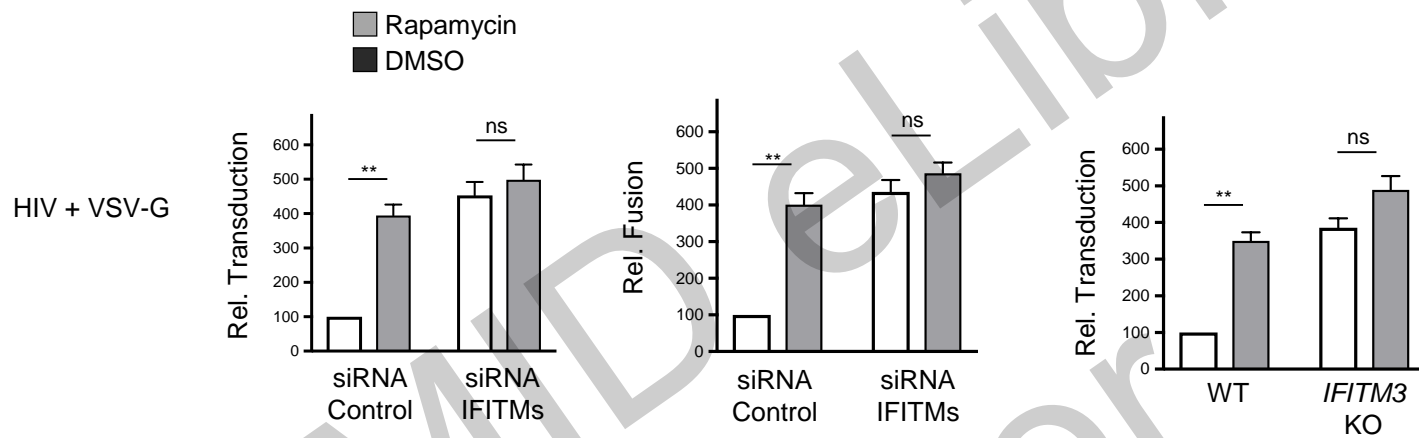
# IFITM3 is targeted to lysosomes by the ESCRT machinery



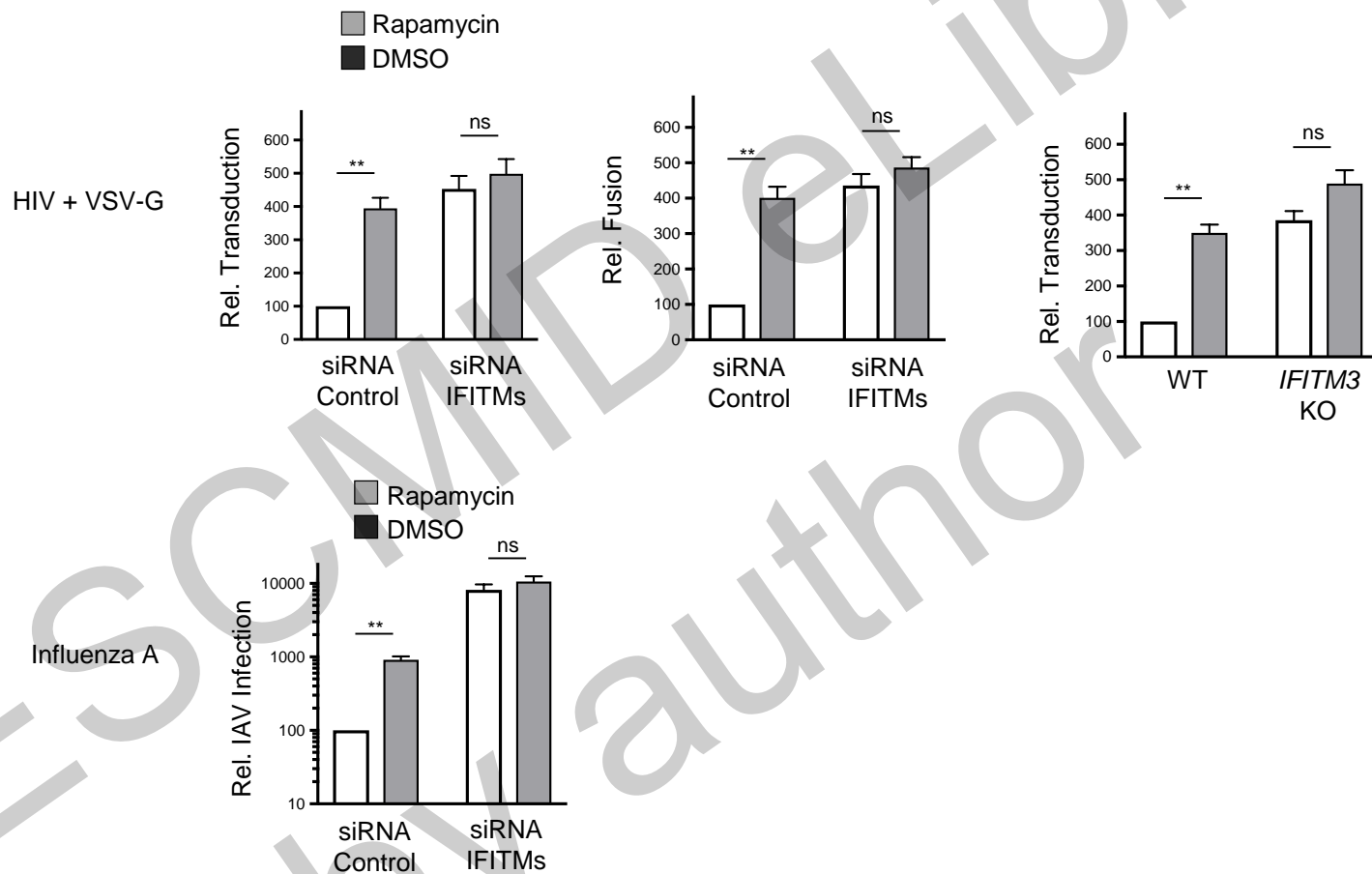
# IFITM3 is downregulated by Rapamycin in CD34+ HSPC



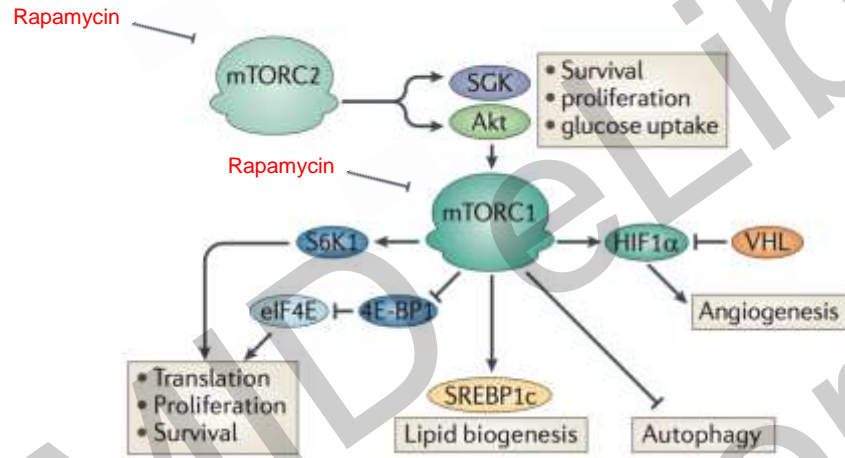
# Rapamycin enhances virus infection due to downregulation of IFITM3



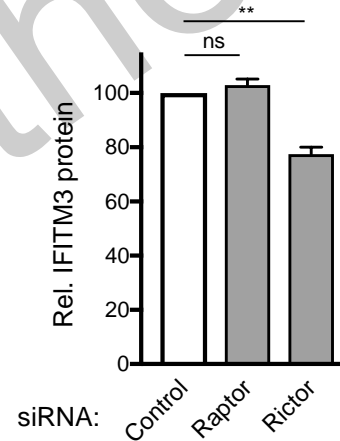
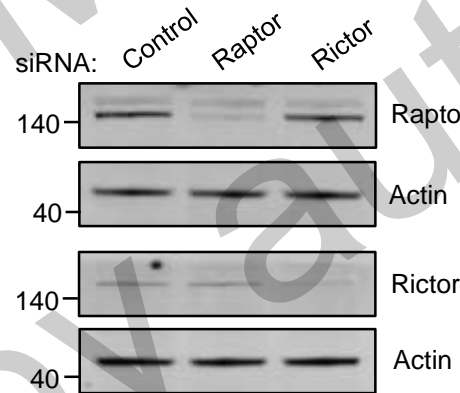
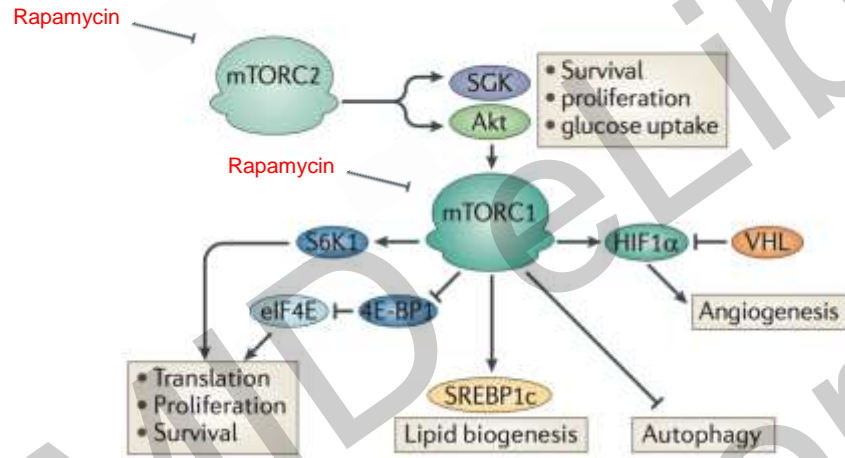
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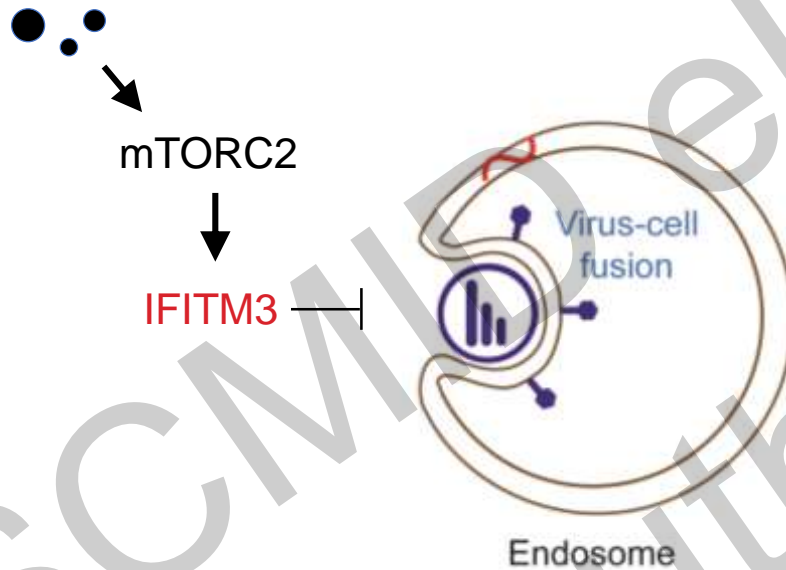
# The mTOR pathway as novel regulator of virus entry



# mTORC2 inhibition results in IFITM3 degradation

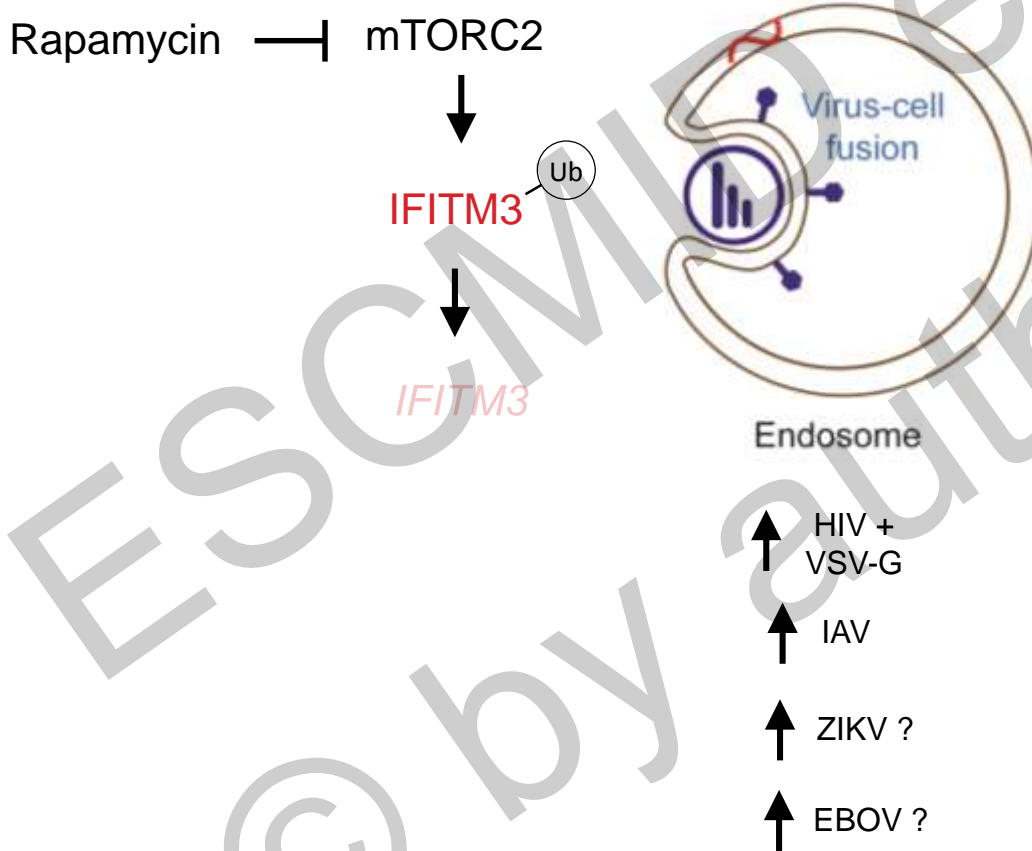


# The mTOR pathway as novel regulator of virus entry





# The mTOR pathway as novel regulator of virus entry



# Acknowledgements

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