

FHL1 is a key host factor for CHIKV infection and pathogenesis

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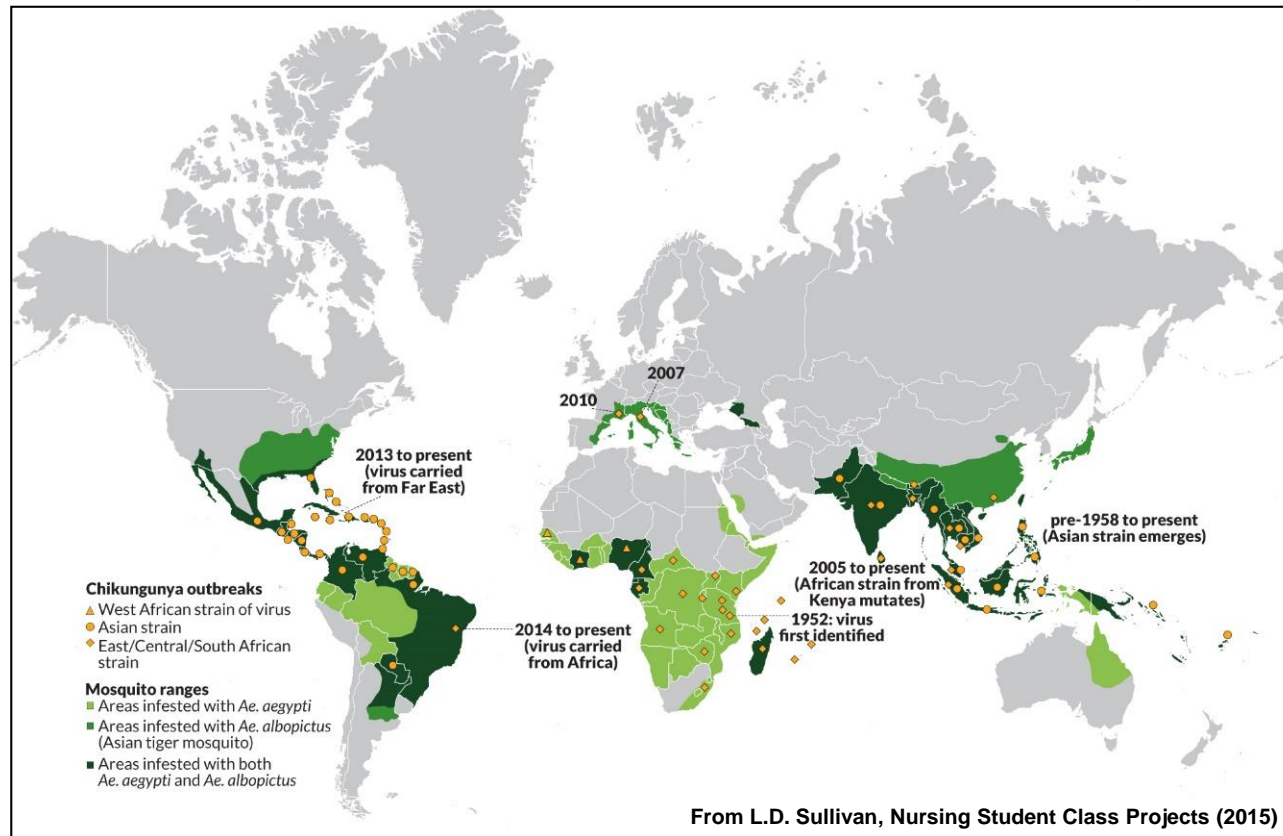
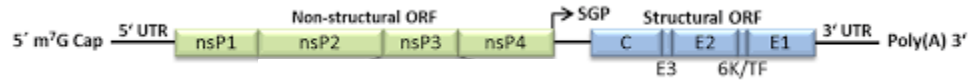
Context of the Research

- Half world population at risk of infection
- Arthropod Borne Viruses
- 3 main viral Families
 - ❖ *Flaviviridae* (flavivirus)
 - ❖ *Togaviridae* (Alphavirus)
 - ❖ *Bunyaviridae* (Bunyavirus, Phlebovirus, Nairovirus)
- Flu-like symptoms to Hemorrhagic fever, meningitis or encephalitis
- No effective vaccine or treatment

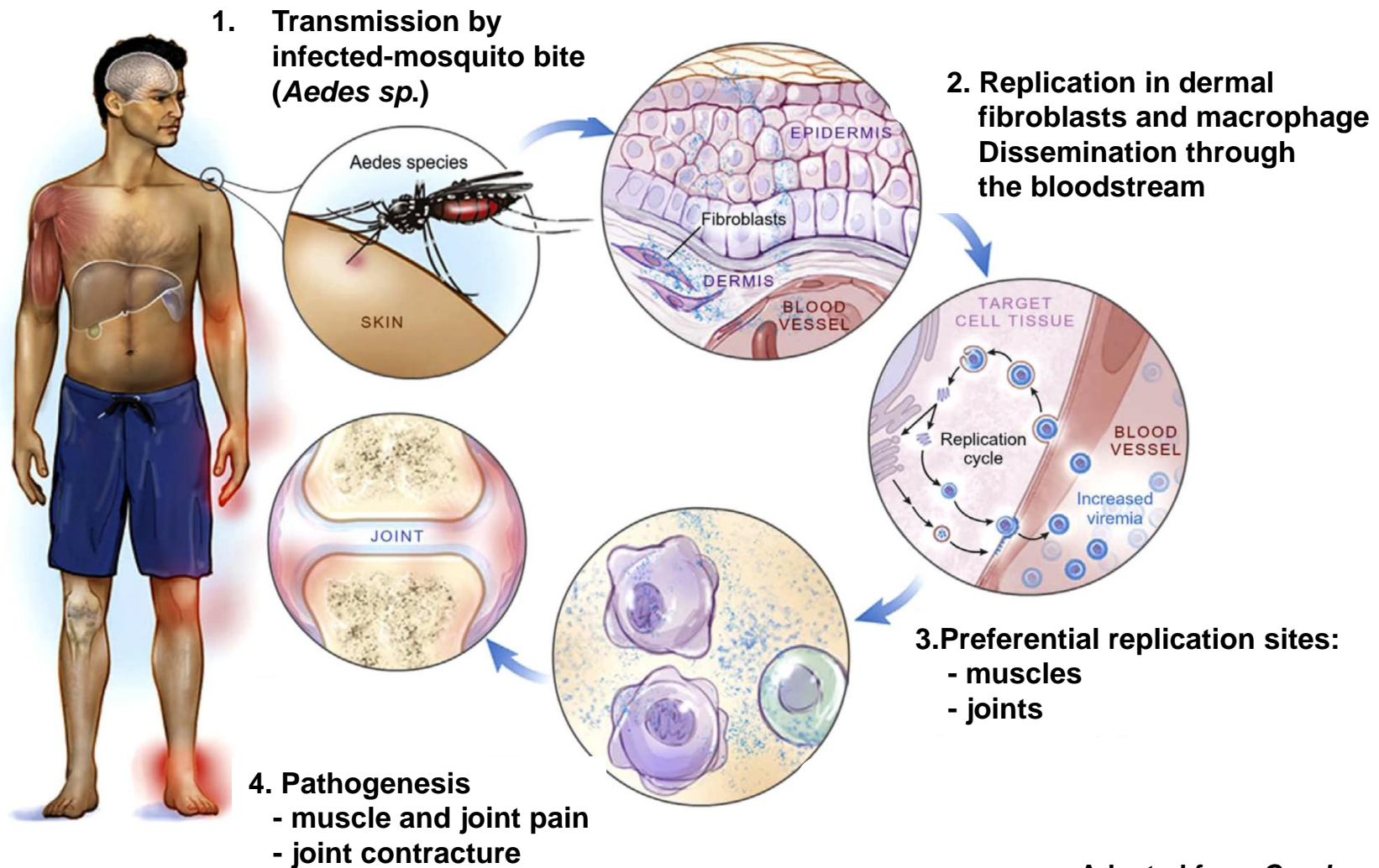
Host Factor = putative therapeutic targets

CHIKV: an emerging and re-emerging virus

- Genus Alphavirus, *Togaviridae* family
- Old World Alphavirus with 3 genotypes (WA, ESCA, Asian)
- ssRNA+



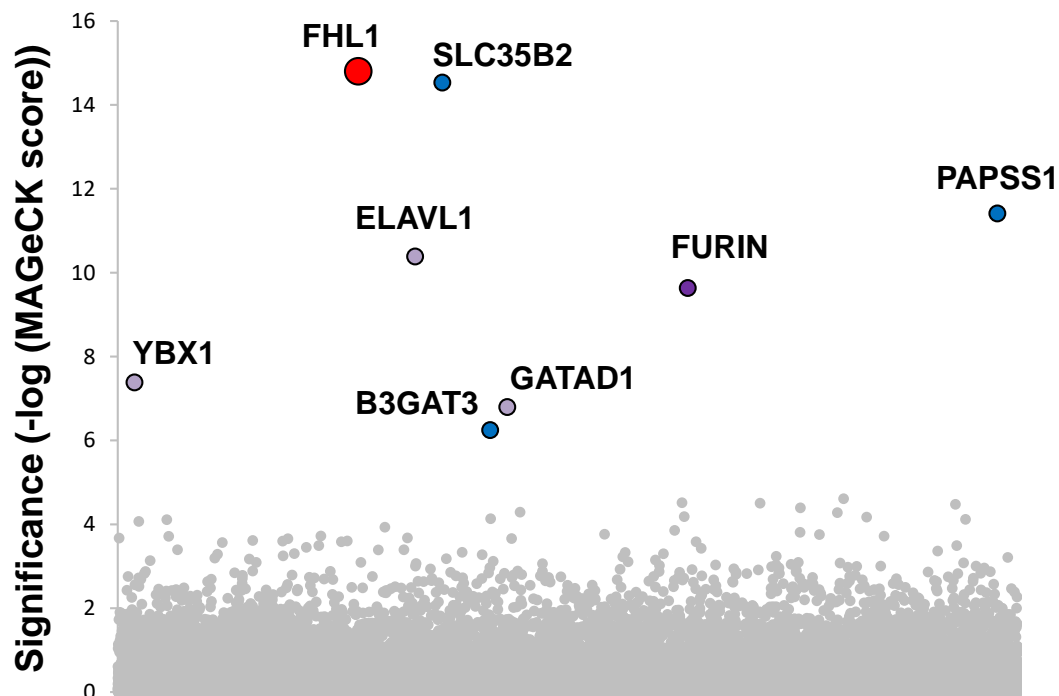
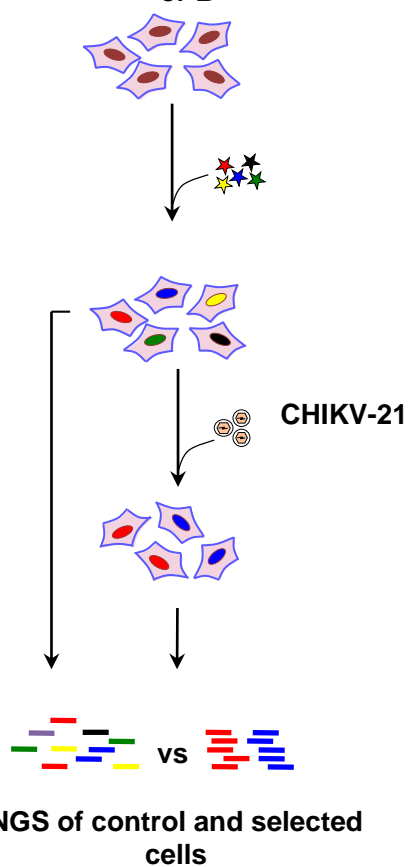
CHIKV tropism and associated pathogenesis



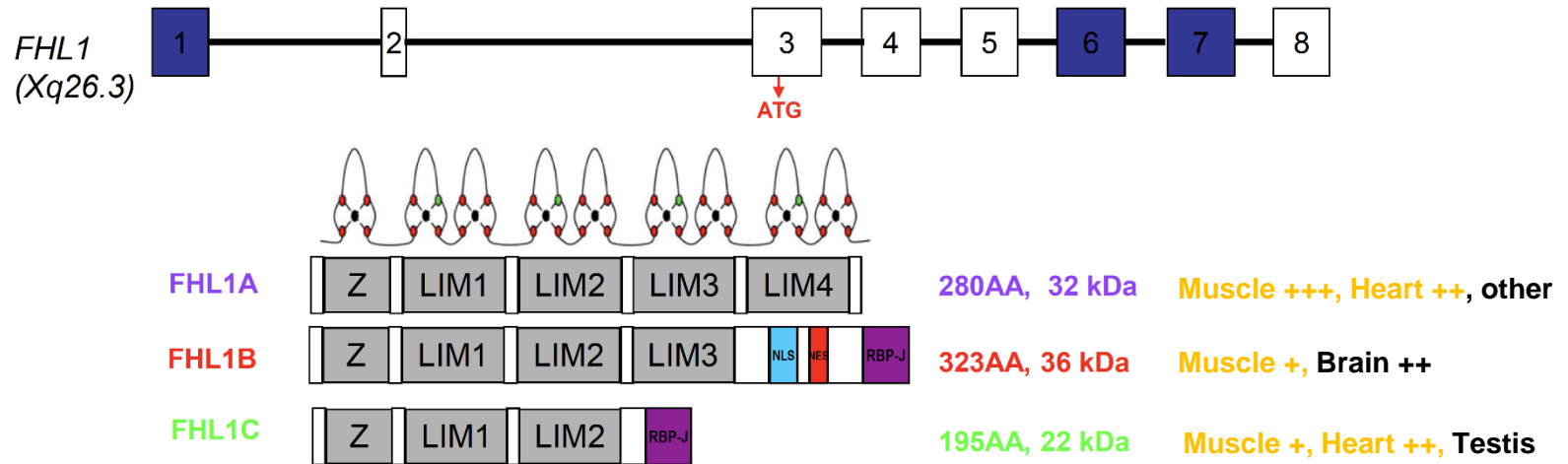
Adapted from *Couderc et Lecuit, 2015*

CRISPR Cas9 screen to identify host genes essential for CHIKV infection

Transduction of HAP1
with pooled lentiviral sgRNA library A
or B



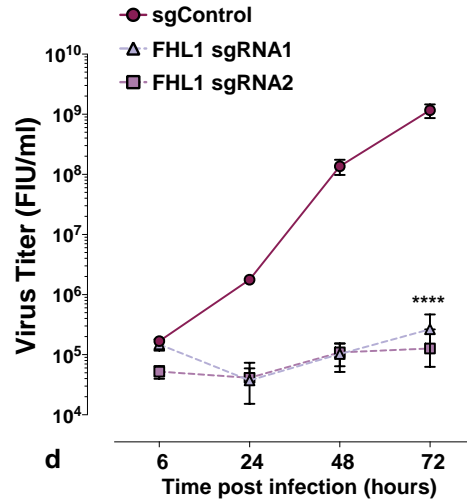
Four and a Half LIM domain protein (FHL1)



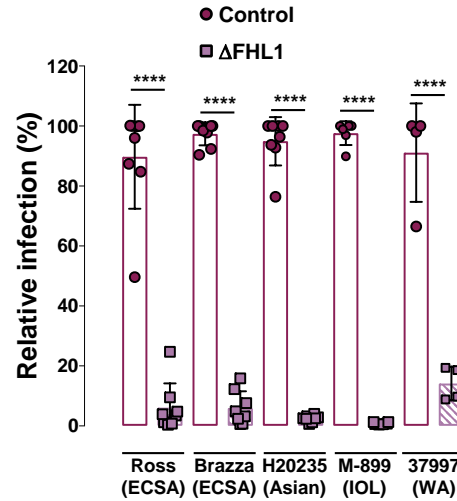
- Localizes to myofibrillar sarcomere and the sarcolemma in skeletal muscles
- May participate in muscle growth and differentiation, sarcomere assembly and it is a regulator of skeletal muscle mass
- Causative gene for 4 distinct human diseases of the muscle
 - Reducing body myopathy
 - X-linked myopathy with postural muscle atrophy
 - Emery-Dreifuss muscular dystrophy
 - X-linked scapulo-peroneal myopathy

FHL1 is important for CHIKV infection

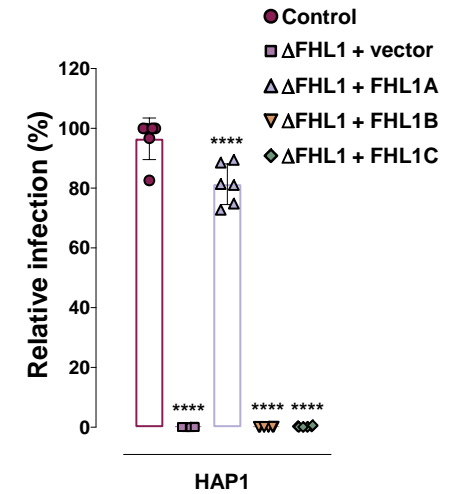
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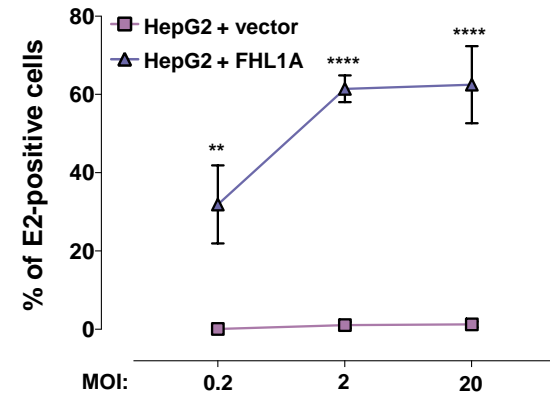
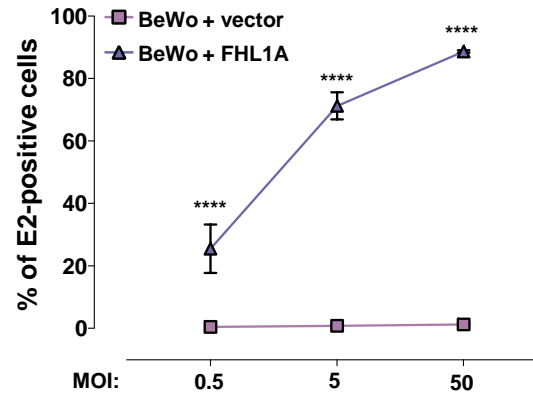
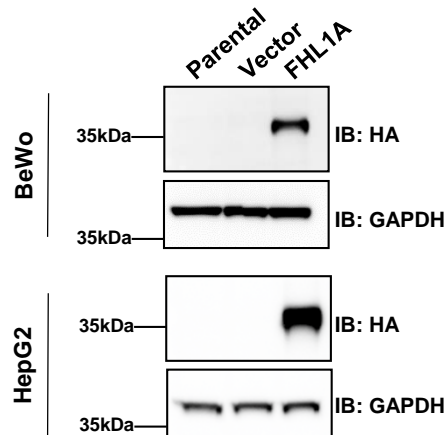
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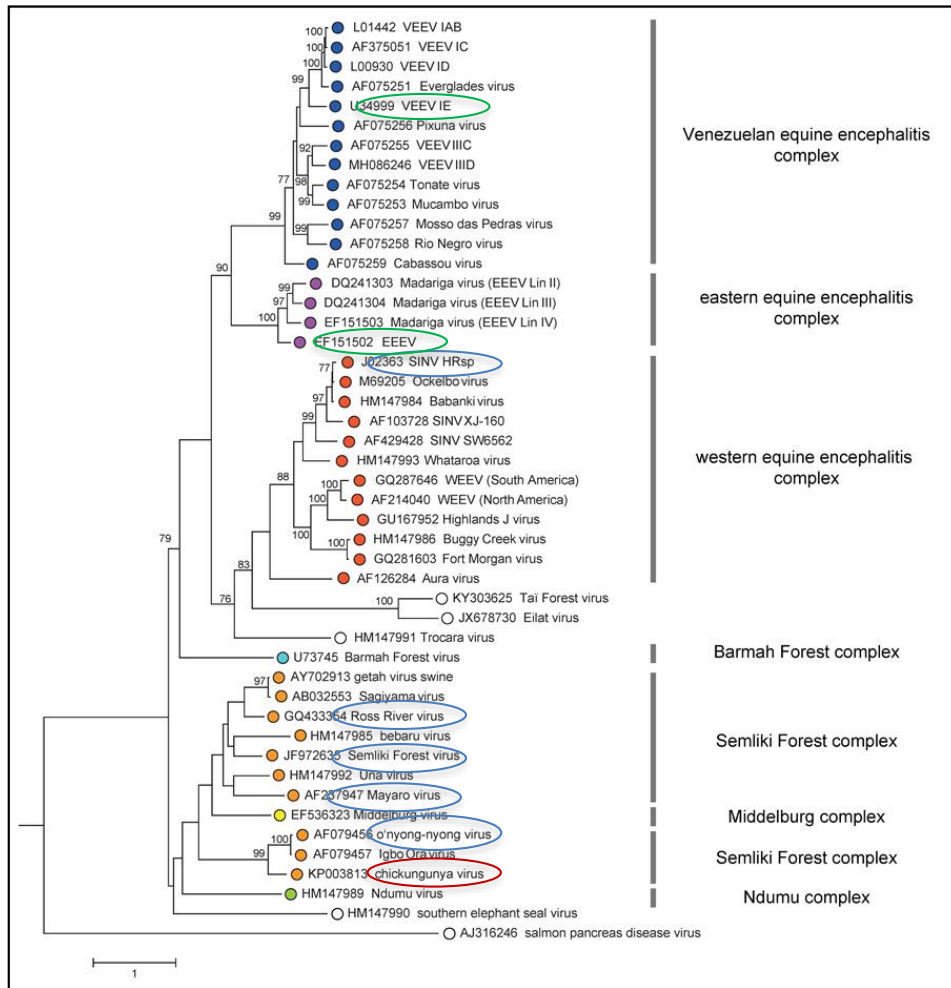
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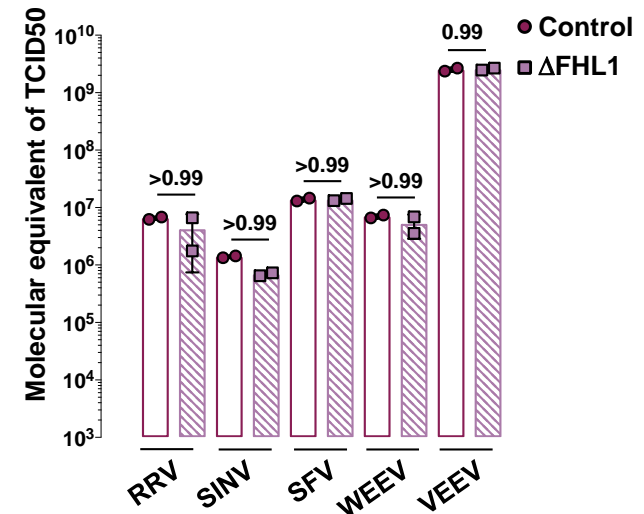
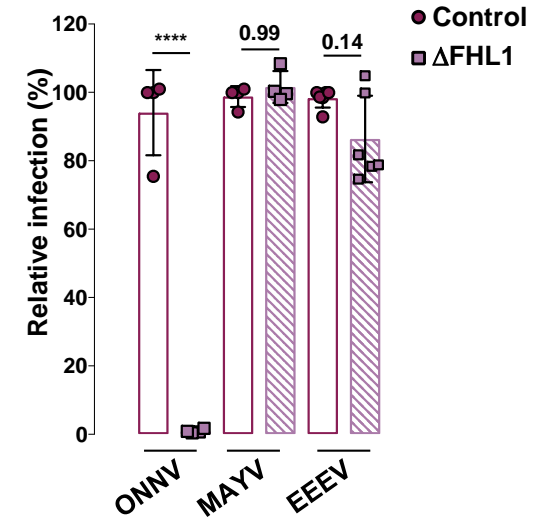
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FHL1 is essential for CHIKV closet relative O'nyong-nyong virus infection



Chen *et al.*; ICTV Virus Taxonomy Profile: *Togaviridae* ; J Gen Virol 2018



FHL1 gene and Emery Dreyfuss disease (EDMD)



F8 (C209R)

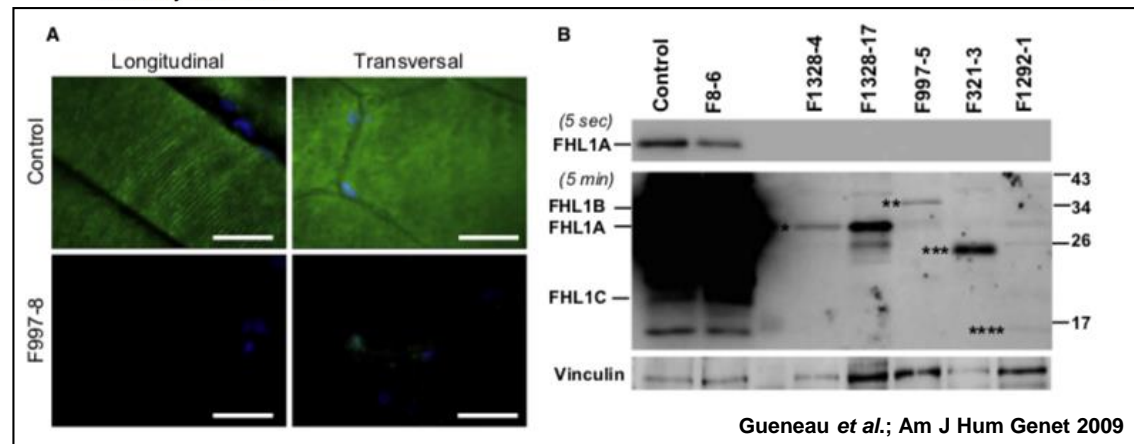
Patient 4, Voit et al. 1988
Courtesy of T. Voit

F997 (X281E)

Courtesy of M. Salih

F1328 (C276Y)

Courtesy of T. Stojkovic

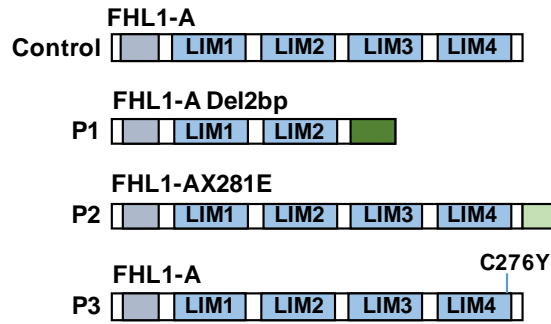


Gueneau et al.; Am J Hum Genet 2009

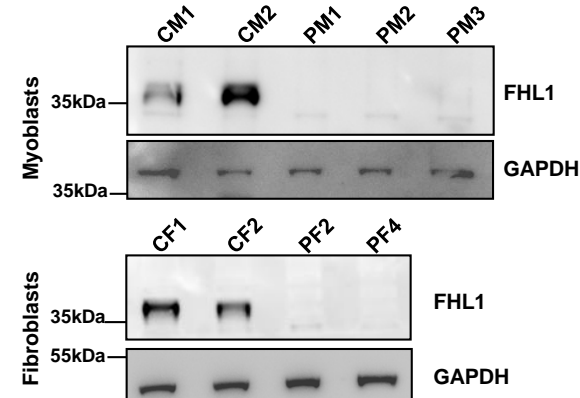
Courtesy of G. Bonne

Primary myoblasts and fibroblasts from EDMD patients are resistant to CHIKV infection

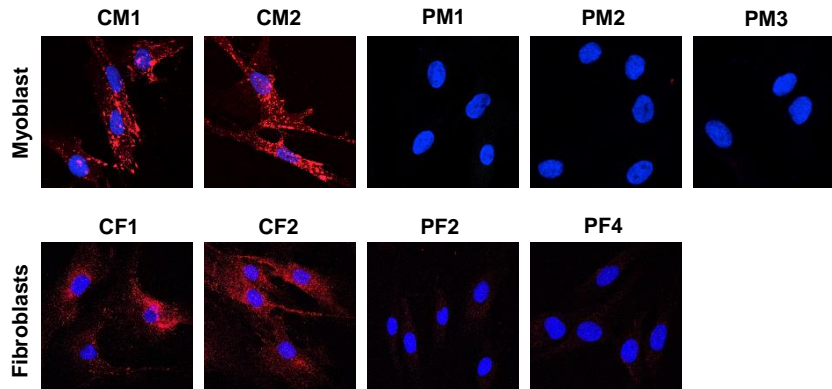
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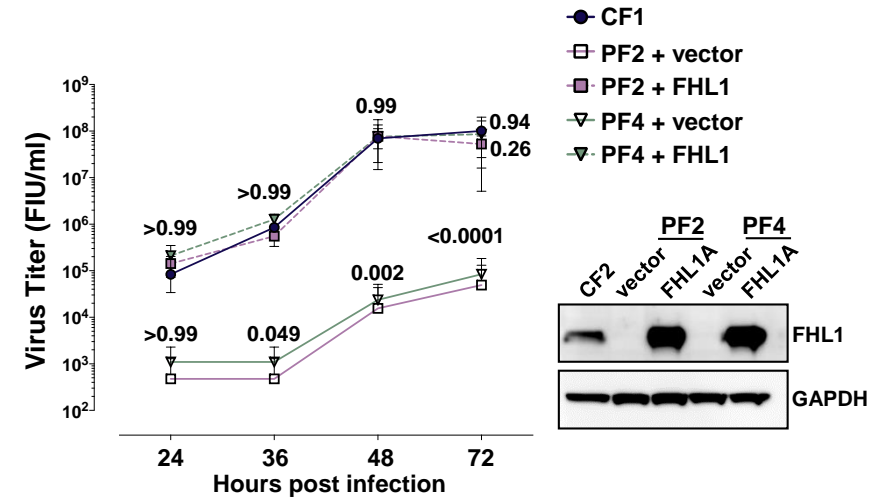
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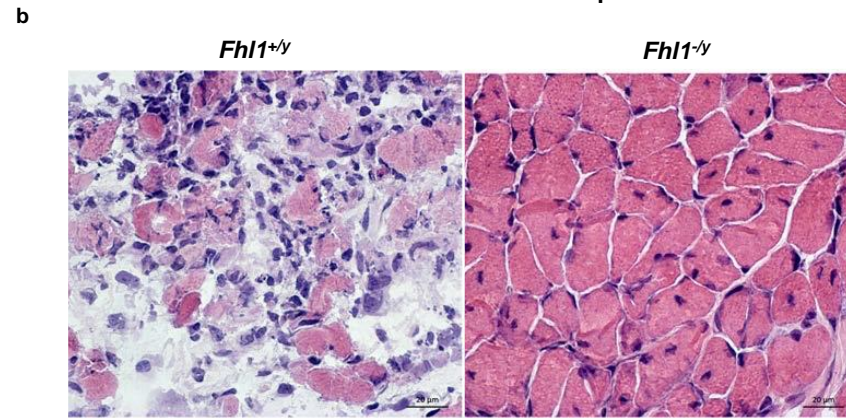
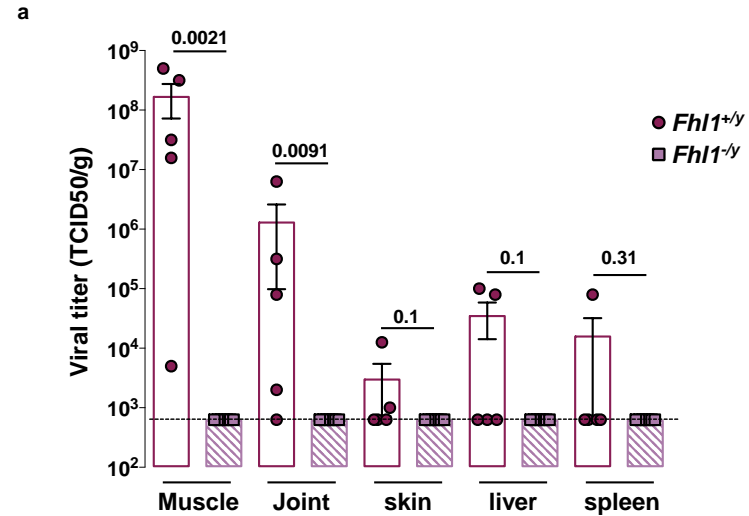
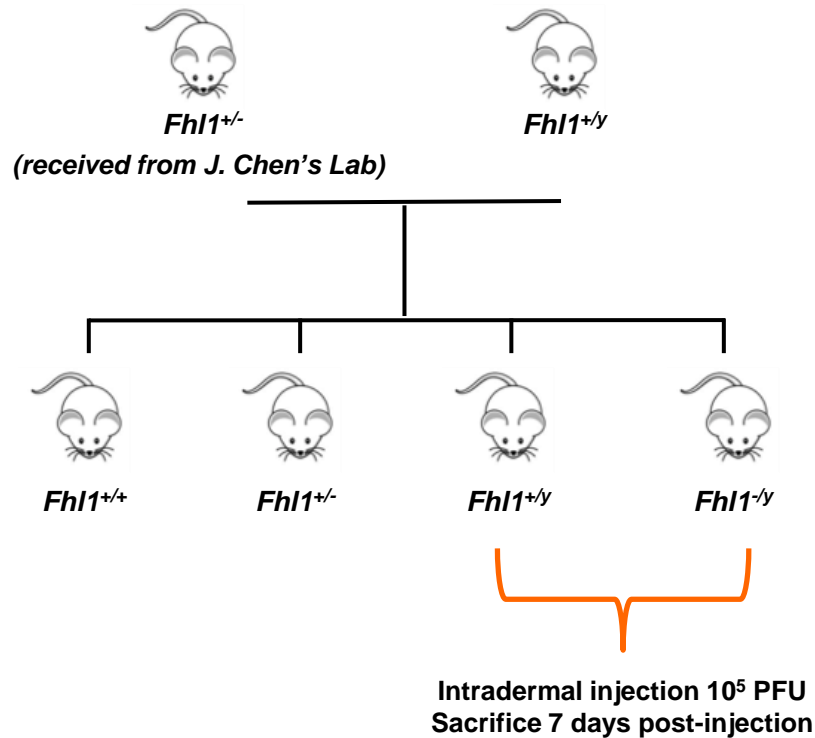


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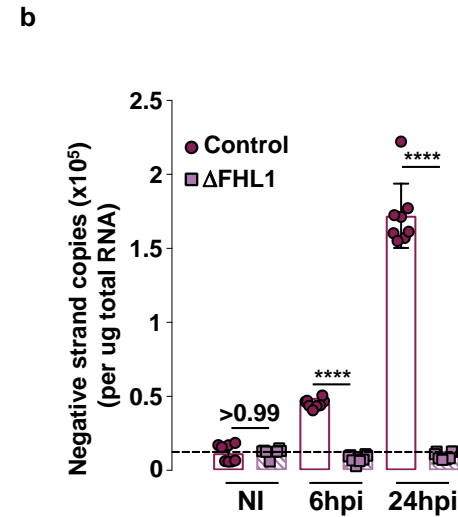
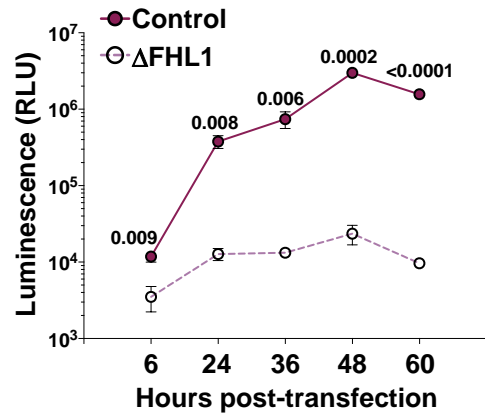
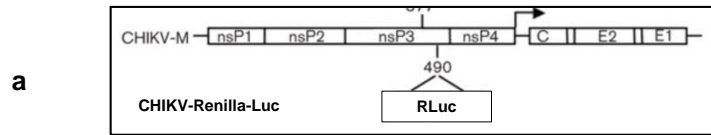


FHL1 is essential for CHIKV replication and pathogenesis in mouse model of infection

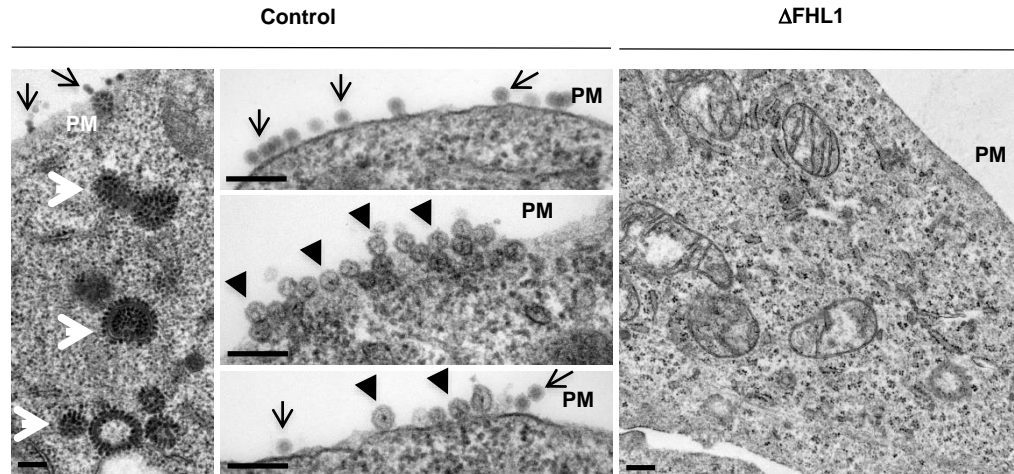
Collaboration with T. Couderc, S. Rafasse, T. Goupil, M. Lecuit (Biology of Infection Unit, Institut Pasteur)



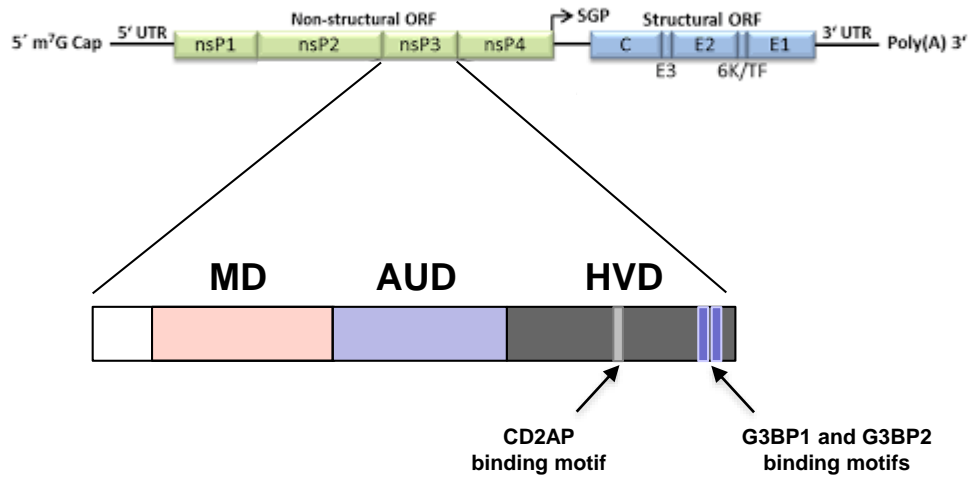
FHL1 is essential for CHIKV replication



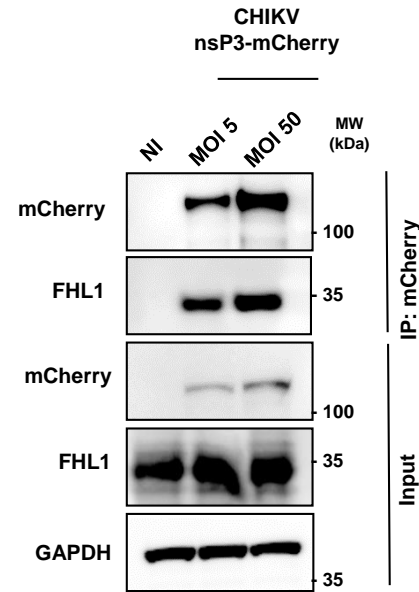
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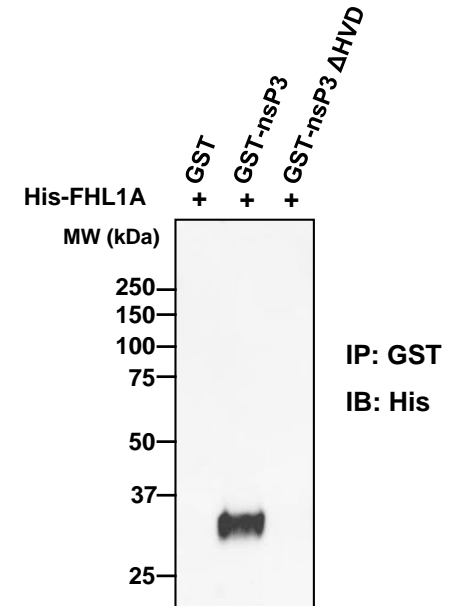
CHIKV nsP3 protein



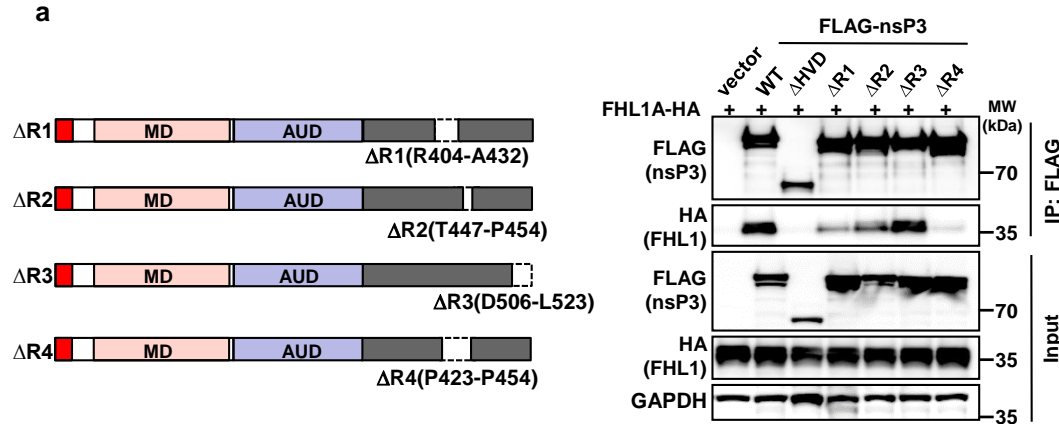
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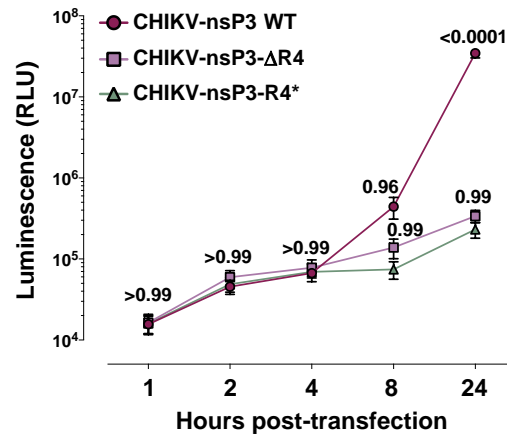


Interaction of FHL1 with nsP3 HVD is essential for its proviral function

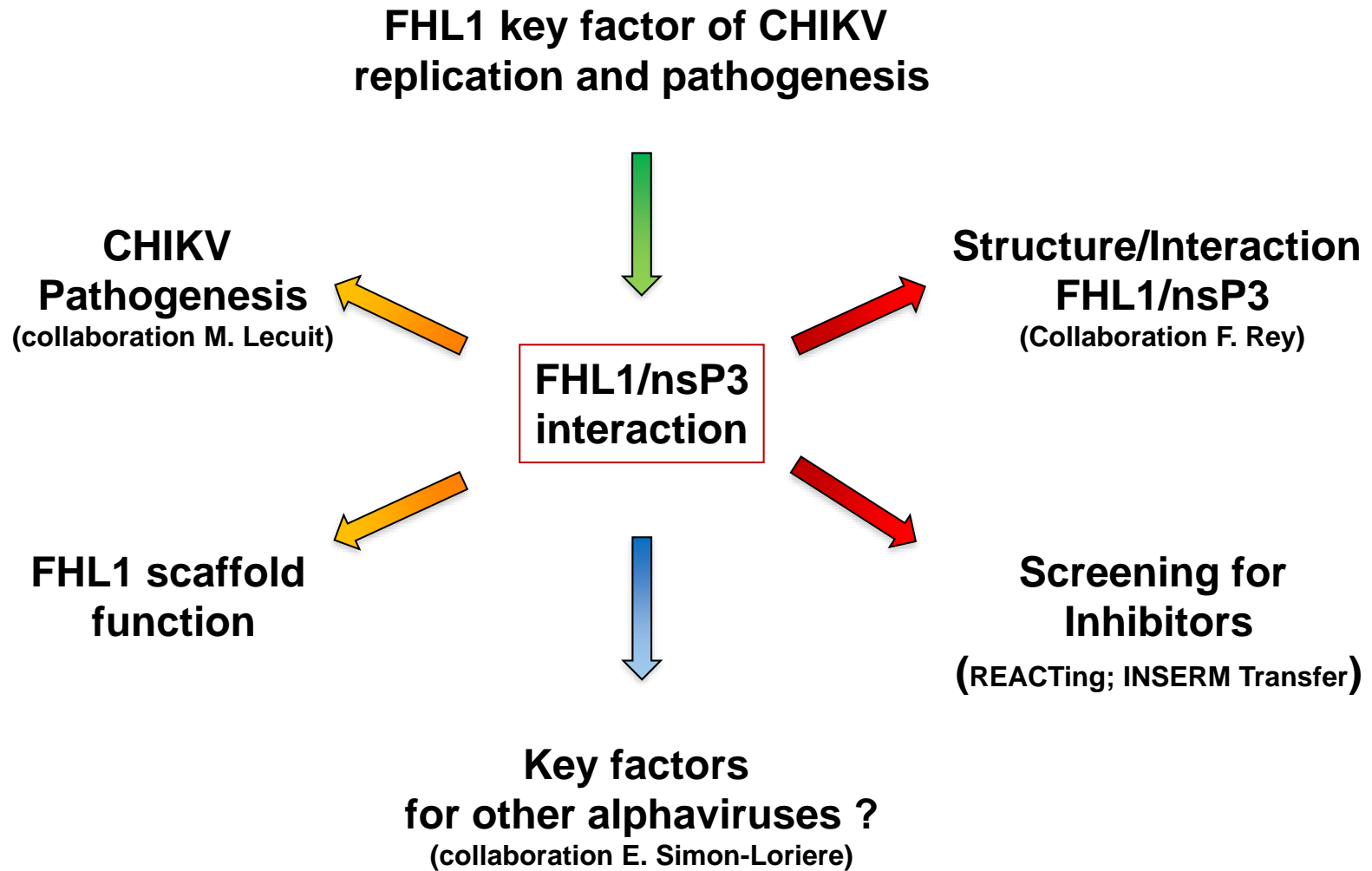


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CHIKV-nsP3-WT PPRRRRGRNLTVTCDEREGNITPMASVRFRAELCPVVQETAETRD TAMSLQAPPSTATE
 CHIKV-nsP3-R4* -----STVPLPALRRASFADTMEQTVAEQFPMCAEVR-----



Conclusion/Perspectives



Acknowledgements

Cell Biology of Virus Infection Team (IRSL)

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