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PERSISTENCE OF CRIMEAN-CONGO HEMORRHAGIC FEVER VIRUS IN THE ENVIRONMENT: MODELING TICK INFECTION WITH HAZARA AND DUGBE VIRUSES.

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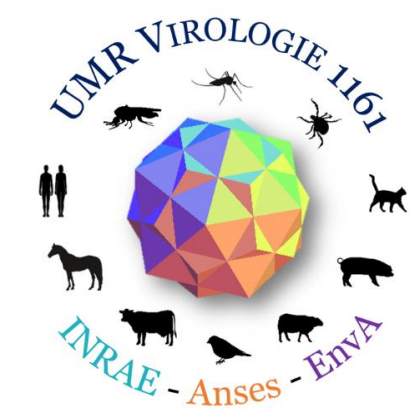
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Background & Objectives

The Crimean-Congo hemorrhagic fever (CCHFV) is maintained in a tick-vertebrate cycle, principally involving ticks of the genus *Hyalomma*.

It is both within and through the tick that CCHFV is maintained and spread in the environment. Indeed, after acquisition of CCHFV, the tick maintains the virus for its entire life span (between 2 and 6 years) and assures its transmission by not only horizontal (from one developmental stage to the following) but also vertical (from the female adult to its offspring) routes.

Thus, in addition to its role as a vector, the tick serves as a reservoir for CCHFV.

Despite the central role of the tick in the biology of CCHFV, these mechanisms have not yet been described.

This project aims to elucidate the molecular mechanisms that permit persistence of CCHFV within ticks of the *Hyalomma* genus.

Because of the constraints associated with handling CCHFV-infected ticks in a biosafety level 4 containment, CCHFV tick infection will be modeled using Hazara (HAZV, JC280) and Dugbe (DUGV, IbAr1792) viruses, which are handled in BSL2 and BSL3 contained facilities, respectively.

Hyalomma infection will be modeled using either *Hyalomma* ticks or *Hyalomma* tick cell lines: HAE/CTVM8 and HAE/CTVM9 derived from *H. anatolicum* embryos and HLE/LULS42 and HLE/LULS43 derived from *H. lusitanicum* embryos.

Task 1 Identification of HAZV-infected *Hyalomma* tissues

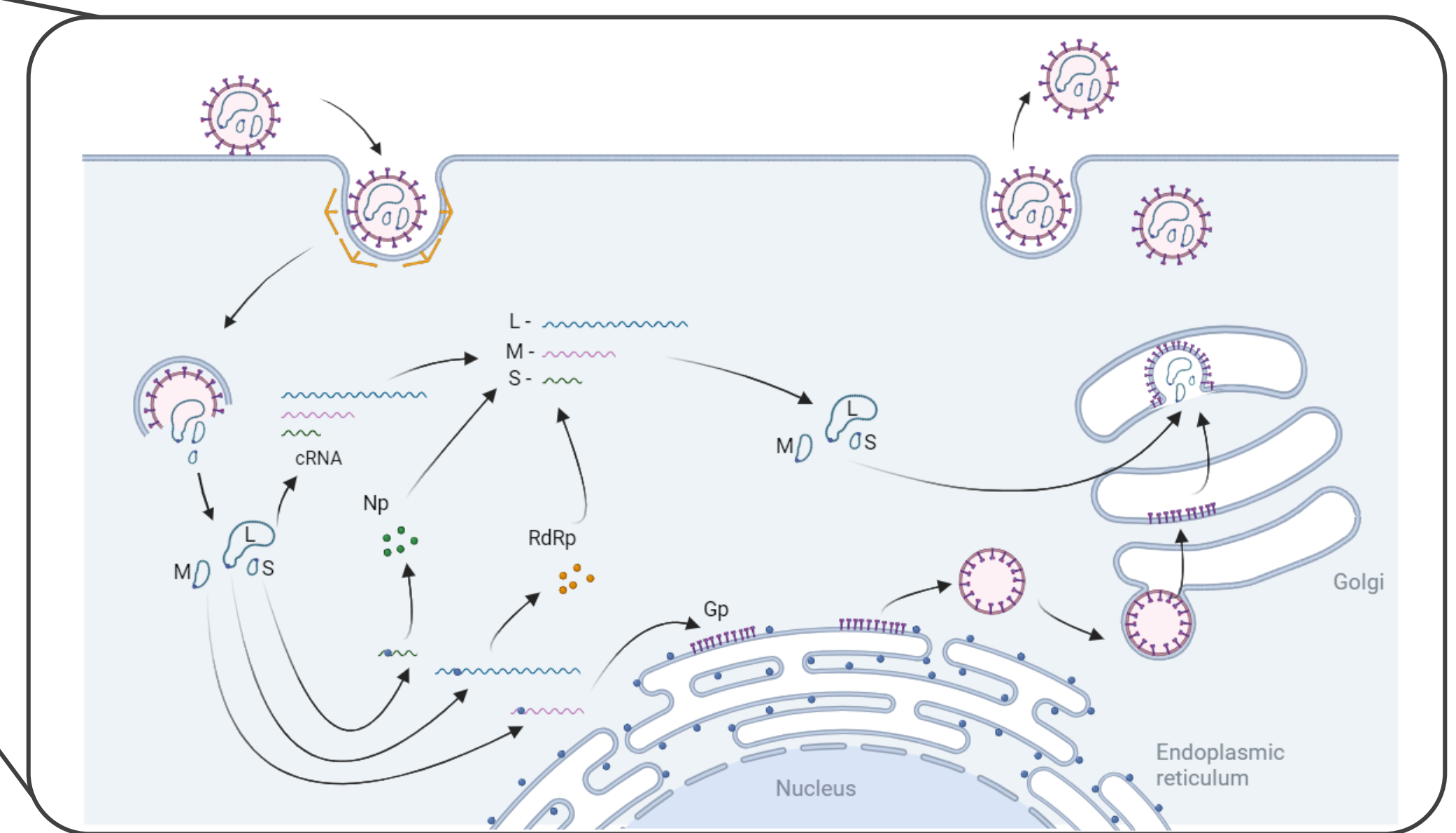
To determine the mechanisms underlying the dual role of the tick, tissues of *Hyalomma* ticks in which the virus persists will be identified as follows:

- As vector: definition of infected tissues that survive the moulting process, persistence of the virus in the salivary glands allowing horizontal transmission of the virus by the tick,
- As reservoir: persistence of the virus in the sexual organs allowing vertical transmission.

To this end, *Hyalomma* ticks will be infected by artificial feeding with an infectious clone of HAZV which expresses a fluorescence reporter gene (rHAZV-eGFP), allowing the course of infection to be followed *in vivo*.

Task 2

Molecular dialogue between HAZV, DUGV and *Hyalomma* tick cells

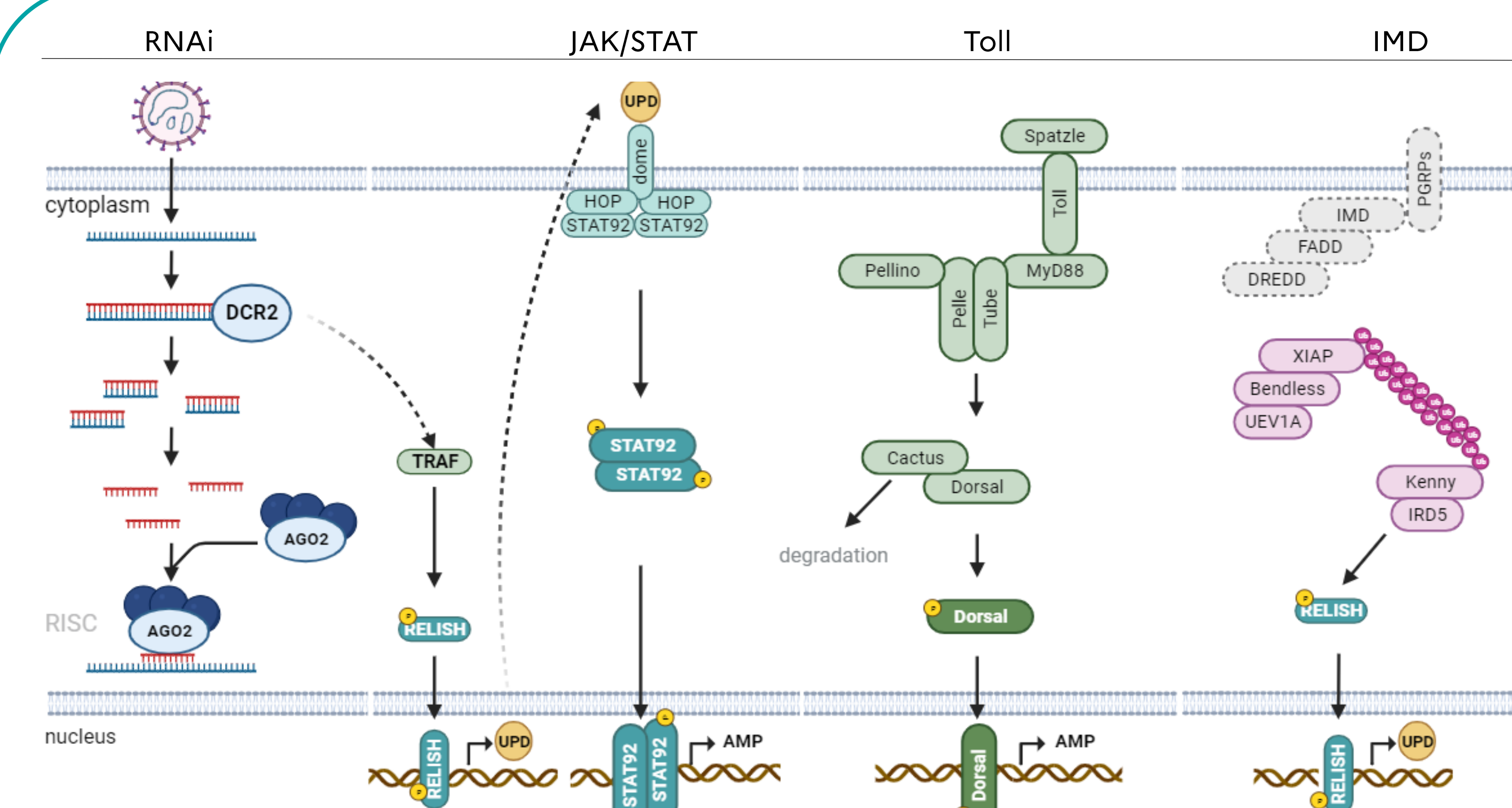


The virus must be capable of surviving without impairment of the life history traits of the tick and of resisting successive moults. As a strict intracellular parasite, the virus hijacks the cellular machinery of its host to ensure its survival, largely through binary interactions between viral components – RNA and proteins – and the tick proteome.

In this task, the molecular dialogue between HAZV, DUGV and ticks of the genus *Hyalomma* will be investigated by establishing the viral protein-tick protein interaction network using an AP/MS strategy and viral genomic RNA-tick protein interaction network using Chirp/MS methodology.

Task 3

Tick antiviral immunity mechanisms



The tick itself does not seem to be affected by viral infection, suggesting that the tick limits viral infection to an acceptable level by deploying an antiviral arsenal.

This task will focus on different antiviral immunity pathways with the objective of identifying those that constrain viral infection and promote persistent infection.

In particular, selected component of the pathways of interest will be silenced in HAZV- and DUGV-infected *Hyalomma* cells, and the impact on HAZV and DUGV replication evaluated.

Task 4 Validation on CCHFV

All protein-protein and RNA-protein interactions, as well as factors from the various antiviral immunity pathways identified as having a pro- or antiviral role in HAZV replication, will be tested for CCHFV.

Expected results

This project will define the tick tissues in which the virus replicates during the different stages of the tick cycle (moulting, reproduction) *in vivo*, and, using tick cell lines *in vitro*, characterize the molecular dialogue (viral protein-tick protein interactions, viral genomic RNA-tick protein interactions, antiviral immune pathways) that enables CCHFV to persist within *Hyalomma* ticks and confers on the *Hyalomma* tick its ability to regulate viral infection, thereby maintaining the virus in the environment and ensuring viral transmission.

The ultimate goal of this project is to instruct development of innovative strategies to deploy in the fight against vector-borne viruses.

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We thank Michèle Bouloy et Pierre-Yves Lozack for their kind gift of HAZV and DUGV. This project is supported by the DIM1Health2.0 and Agence de l'Innovation de Défense (thesis funding) and by Laboratoire d'Excellence Intégrative Biology of Emerging Infectious Diseases (postdoctoral position funding).

