Structural basis for the membrane fusion step in Hantavirus entry

ShT.3.5-001

W. Shmuel [I], H. Bar-Rogovsky[I], E.A. Bignon[II], N.D. Tischler[II], Y. Modis[III], **M. Dessau** [IV]

[I]The Faculty of Medicine in the Galilee, Bar Ilan Univesity, Safed, Israel, [II] Molecular Virology Laboratory, Fundación Ciencia & Vida, Santiago, Chile, [III]Dept. of Medicine, University of Cambridge, MRC Laboratory of Molecular Biology, Cambridge, United Kingdom, [IV]The Faculty of Medicine in the Galilee, Bar Ilan University, Safed, Israel

Hantaviruses are important emerging human pathogens and are the causative agents of serious diseases in humans with high mortality rates. Like other members in the *Bunyaviridae* family their M segment encodes two glycoproteins, G_N and G_C, which are responsible for the early events of the viral infection. Hantaviruses deliver their tripartite genome into the cytoplasm by fusion of the viral and endosomal membranes in response to the reduced pH of the endosome. Unlike phleboviruses (e.g. Rift valley fever virus), that have an icosahedral glycoprotein envelope, hantaviruses display a pleomorphic virion morphology as G_N and G_C assemble into spikes with apparent four-fold symmetry organized in a grid-like pattern on the viral membrane. We determined the crystal structure of glycoprotein C (G_C) from Puumala virus (PUUV), a representative member of the *Hantavirus* genus. The crystal structure shows G_C as the membrane fusion effector of PUUV and it presents a class II membrane fusion protein fold. Furthermore, G_C was crystallized in its post-fusion trimeric conformation that until now had been observed only in *Flavi-* and *Togaviridae* family members. The PUUV G_C structure together with our functional data provides new mechanistic insights into class II membrane fusion proteins and reveals new targets for membrane fusion inhibitors against these important pathogens. Both similarities and differences to other class II membrane fusion proteins implies a revise paradigm for the evolution of these unique proteins.