Deciphering the unconventional receptor binding and modulation activity of the bat influenza A virus surface glycoproteins (ERC funded project)

(Two PhD positions)

Influenza A viruses (IAVs) are zoonotic pathogens that frequently cross the species barrier into humans, often causing severe morbidity and even global pandemics. This cross-species transmission is facilitated in large part by alterations in the interaction between the viral surface proteins hemagglutinin (HA) and neuraminidase (NA) and sialic acid, a ubiquitous glycan that serves as the cellular entry receptor. Although avian hosts have generally been thought to be the primary reservoir for all influenza A viruses, this dogma has recently been challenged by the identification of two novel IAV subtypes in bats, H17N10 and H18N11 (Ciminski et al. (2020), PLoS Pathog. 16;16(4):e1008384).

Despite an otherwise high degree of functional homology to conventional IAVs, the surface proteins of bat IAVs demonstrate several unprecedented characteristics. Specifically, these proteins are unable to interact with sialic acid; rather, we recently showed that bat IAV HAs use the major histocompatibility complex class II (MHC-II) protein to gain entry into host cells (Karakus et al. (2019) Nature, 567:109-112). Moreover, we observed that N11 NA downregulates surface expression of MHC-II, suggesting that it potentially harbors a receptor-destroying function. Most surprisingly, following serial passaging bat IAV variants with increased replication properties emerged that encoded mutations in the H18 HA head domain together with a truncated N11 NA. As determined by reverse genetics, the HA mutations enabled replication in the absence of functional NA, suggesting that the surface glycoproteins of bat IAV may possess a structural plasticity that is much broader than that of conventional IAVs (Ciminski et al. (2020), Nat Microbiol. 4:2298-2309).

In light of the critical importance of the surface proteins for cross-species transmission of IAV, the goal of this project will be (i) to determine the mode of interaction between H17/H18 and MHC-II, (ii) elucidate the mechanism of N10/N11-dependent downregulation of MHC-II, and finally (iii) to probe their plasticity by forced evolution approaches that will explore the additive potential of IAV for new cellular entry factors. The insights from these studies will have a major impact on our understanding of influenza virus tropism, virus evolution and the development of novel therapeutic methods.