might mimic GAPR-1. However, how Nef inhibits autophagy remains unclear because previous studies have shown that it does not exclusively localize to the Golgi, suggesting that binding and inhibition of beclin 1 may be much more complicated than merely sequestering it to the Golgi. Thus, binding of both Nef and GAPR-1 to beclin 1 may inhibit autophagy through additional mechanisms not described by Shoji-Kawata *et al.*[1]. For example, when the authors expressed a mutant version of beclin 1 that lacked the GAPR-1–binding site, which would be expected to enhance autophagy, it actually reduced the induction of autophagy.

The region of beclin 1 bound by Nef is located in the evolutionarily conserved domain of the protein, which is also bound by the previously known partner of beclin 1, Vps34. However, the authors found that deleting the Nef-binding site did not affect Vps34 binding. Therefore it appears that Nef-mediated inhibition of autophagy may not act by blocking the binding of beclin 1 and Vps34.

Interestingly, the authors highlighted two conserved aromatic residues within their Nef-binding sequence that are critical for binding GAPR-1 and the autophagy-inducing function of their peptide. Recent studies investigating the crystal structure of the evolutionarily conserved domain have revealed the presence of three aromatic amino acids that associate with lipid membranes and cause deformation of membrane and liposomes[6]. Mutations in these aromatic residues inhibited beclin 1 from binding membranes and prevented autophagy rescue in beclin 1 knockdown cells[6]. Further studies are needed to explore whether Nef and GAPR-1 may also prevent the binding of beclin 1 to lipid membranes by blocking aromatic residues in the Nef binding sequence.

Beyond these exciting new revelations about intracellular autophagy mechanisms, the obvious question is whether the peptide of Shoji-Kawata *et al.*[1] can ameliorate any of the myriad conditions associated with deficits in autophagy. Using a cell culture model that mimics protein aggregation seen in Huntington's disease, the authors found that treatment with the peptide promotes the clearance of small aggregates (**Fig. 1**). These findings are consistent with previous studies demonstrating a critical role for autophagy in the clearance of protein aggregates associated with Huntington's[7], Parkinson's[8] and Alzheimer's[9] diseases. Moreover, the peptide effectively inhibited the replication of four viruses, including HIV, and the intracellular bacterium *Listeria monocytogenes*.

In vivo studies showed that intraperitoneal delivery of the peptide enhanced the survival of mice infected with either West Nile or chikungunya virus (**Fig. 1**). Chikungunya virus primarily infects fibroblasts and is found in muscle, skin and joints. Notably, West Nile virus is a neurotropic virus that primarily infects neurons. Characteristic changes in brain tissue indicative of enhanced autophagy suggested that the peptide crossed the blood-brain barrier and modestly induced autophagy. These results are encouraging for the potential treatment of neurotropic virus infection and neurodegenerative disease, but caution is warranted because the experiments were performed in 5-day-old mice, whose blood-brain barrier may be more permeable than that of adults. Future studies must confirm that the peptide reaches the adult brain and is well tolerated.

Measurements of weight, kidney function, liver function and blood cells suggested that the treated mice were healthy, but potential toxicity of the peptide requires further evaluation. Indeed, the function of GAPR-1 is currently unknown, as are the consequences of a peptide that binds and possibly inhibits it. Moreover, autophagy is thought to be involved in cell death[10,11], and it is not clear whether prolonged treatment with the peptide could provoke autophagic cell death.

If the peptide meets initial requirements on the drug-development pathway, it may be possible to design small-molecule mimics that bind the same site on GAPR-1 but have optimal half-lives and binding kinetics. From this perspective, the study of Shoji-Kawata *et al.*[1] provides a framework for the identification of other potential disease-modifying targets based on decoding how viruses engage critical proteins within a pathway of interest.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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