

Evolution

- Every possible benefit of GOF studies presumes that what we see in a lab strain will be predictive of what will happen in natural strains

Will GOF mutations work the same in nature as in the lab? Not likely

- EPISTASIS: small changes in genetic background change the effect of our mutations of interest
 - Tharakamaran et al. 2013 *Cell*: GOF mutations do not confer human binding on H5 from Egyptian strains
 - Flu E627K PB2: long known to be associated with increased transmissibility and virulence. This turned out to be false for 2009 H1N1pdm
 - Flu NA H275Y resistance mutation was crippling to H1N1 virus in ferrets. Never spread. UNTIL 2007-8. Genetic background of circulating strain changed, suddenly H275Y was advantageous and the resistant strain spread globally within a year!
 - Similar story in adamantane resistance and H3N2

Ethics

- Many proponents of GOF suggest we must not prohibit any scientific experiment, because we can never know what experiments will be useful.
- We live in a world where almost all scientific experiments are effectively prohibited by FUNDING, ethical restrictions, and sometimes safety concerns.
- These experiments, to create an almost unprecedented combination of transmissibility and virulence, should be subject to much tighter scrutiny than a typical experiment: “we might learn something” is not good enough!