reassortment were detected. Some recombinant segments had unusual organizations with 2 intergenic regions. This genetic fluidity is closer to that observed in influenza viruses than to the relatively placid genomics of mammalian arenavirus. However, the observed imbalance between the S and L segments and the intrahost accumulation and persistence of multiple genotypes is previously undocumented. Overall, this provides an opportunity to study basic mechanisms of viral adaptation and stretches the idea of what it means to be infected by “a virus”.

http://dx.doi.org/10.1016/j.nhtm.2015.07.031

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http://dx.doi.org/10.1016/j.nhtm.2015.07.032

Preemption, the Virus-Serum-Toxin Act, and the USDA: a case study using iatrogenic abortion due to BoHV-1 vaccines in pregnant cows

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Three major vaccine manufacturers in the United States currently sell multivalent vaccines containing modified live bovine herpesvirus 1 (BoHV-1) for use in pregnant cattle. The first of these products entered the US market in 2003. Yet it has been known since the early 1960s that vaccinal BoHV-1 causes abortion in cattle. The products became popular as they can be used year-round, regardless of pregnancy status in herds. Abortifacient effects have been considered to be minimal, provided initial vaccination is done during the previous 12 months using specific vaccine products and in accordance with label directions. Single nucleotide polymorphisms (SNPs) in BoHV-1 can be used to resolve whether post-vaccination outbreaks of abortion in cattle herds are iatrogenic (Fulton et al.; Vaccine. 2013; 31(11):1471-1479). We tested tissues from 10 abortion episodes (2010–2014) where an apparent association existed between recent use of modified live BoHV-1 and abortion 1–3 months later. Products were used on or off label in individual outbreaks. All 10 episodes had SNP patterns consistent with those of commonly-used modified live BoHV-1 strains (O'Toole et al.; Vet Pathol. 2014, In press). In spite of this, it is likely such products will remain on the market. This is due the absence of meaningful post-marketing surveillance of suspect adverse reactions in animals by the USDA, compounded by the courts’ interpretation of the Virus-Serum-Toxin Act of 1913 [Lynnbrook Farms v. SmithKline Beecham Corp., 79 F.3d 620 (7th Cir.).] Interesting differences exist between the handling of adverse vaccine reactions in human patients through the National Vaccine Injury Compensation Program (VICP), and similar reactions in animals following use of federally licensed vaccines.

http://dx.doi.org/10.1016/j.nhtm.2015.07.033

Structure-based Engineering of Sabin 2 Poliovirus Polymerase to Alter Replication Fidelity

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Picornaviruses cause a wide range of ailments, including myocarditis, poliomyelitis, and vesicular lesion type diseases. Excellent vaccines exist for several of them, and the development of the live-attenuated oral polio vaccine (OPV) provided an efficient and cost-effective avenue for successful poliovirus eradication in the majority of the world. However, one hurdle for developing successful live-attenuated vaccines lies with the viral RNA-dependent-RNA-polymerase (RdRP) enzyme whose low replication fidelity allows for reversion of attenuated viruses to disease causing variants. Improving the replication fidelity of RdRPs is an attractive avenue for virus attenuation because it may curtail such reversion issues. We have previously solved the crystal structures of several picornaviral polymerase-RNA complexes that show the structural changes taking place within these polymerases during active site closure and catalysis [Gong et al., 2010, 2013]. Based on this, we engineered a panel of fidelity variant coxsackievirus B3 polymerases that caused reduced infectivity and attenuated virus growth in mice (Gnädig et al., 2012). We hypothesize that such modulation of polymerase fidelity via structure based protein engineering can provide an effective platform to improve the design of live-attenuated vaccines. To investigate this further we have generated over a dozen mutations in the poliovirus Sabin 2 strain polymerase and carried out in vitro biochemical assays to show that these can either increase or decrease polymerase fidelity while having minor effects on elongation rates and processivity. The fidelity modulation can arise from single point mutations, multi-site mutations that replace entire groups of interacting residues, or from grafting in structurally homologous sequences from related polymerases. The data suggests mutations in the palm domain of the poliovirus RdRP can serve as efficient fidelity modulation sites for protein engineering purposes, and we are now seeking to test these variant polymerases in an infectious virus context.

http://dx.doi.org/10.1016/j.nhtm.2015.07.034

Generating new prions by targeted mutation or segment duplication

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Prions are infectious agents composed entirely of protein. Prion activity results from the conversion of soluble proteins into an insoluble, self-templating amyloid form. Nine different amyloid-based prions have been identified in yeast. All but one contain a glutamine/asparagine (Q/N) rich region that is responsible for prion activity. Similar Q/N-rich regions are over-represented in eukaryotic genomes. In humans, aggregation-mutation in Q/N-rich proteins have been linked to various degenerative diseases, including ALS. Our lab previously developed a prediction algorithm, PAPA (Prion Aggregation Prediction Algorithm), to predict the aggregation propensity of Q/N-rich proteins, and to predict the effects of mutations on aggregation propensity. Here, we tested the ability of PAPA to design mutations to turn non-prion proteins into prions. We identified four yeast Q/N-rich protein fragments that lacked any detectable aggregation or prion activity. In each case, a small number of designed mutations were sufficient to cause these domains to aggregate, and in two cases, to create bona fide prion activity. We then tested whether simply generating tandem repeats of short, aggregation-prone segments within these domains would likewise be sufficient to create