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Abstract intended for SMBE, Chicago, July 2013:

Title: Reconstructing the highly virulent Classical Swine Fever Virus strain Koslov

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Classical swine fever virus (CSFV) may be highly virulent in pigs with a mortality rate close to 100%. The CSFV “Koslov strain” is known to be one of the most virulent CSFV, but so far a functional cloned cDNA of this strain has not been described. We suggest that this may be due to the error-prone nature of the RNA-dependent RNA polymerase resulting in the majority of circulating forms being non-functional. However, since any infectious virus particle should necessarily be the offspring of a functional virus, we hypothesized that it should be possible to synthesize a highly virulent form by reconstructing ancestral sequences. To test this hypothesis, we inferred sequences that correspond to ancestral nodes in a phylogenetic tree built from full-length nucleotide sequences of non-functional Koslov cDNAs and then proceeded to test the reconstructions. Specifically, we altered a non-functional cDNA by site directed mutagenesis, removing non-synonymous mutations step by step. In vitro testing of modified constructs did indeed lead to fully functional viruses with similar growth kinetics as the wild-type strain. Moreover, viruses rescued from the construct had the ancestral amino acid sequence and, when tested in pigs, were at least as virulent as the Koslov strain. The ancestral reconstruction therefore proved to give rise to a functional cDNA of the highly virulent Koslov strain. In vivo studies confirmed our methods and enabled us to identify nucleotide positions within the viral genome important for virulence.