African Swine Fever Virus (ASFV) is a high-consequence Transboundary Animal Disease pathogen that often causes hemorrhagic fever in pigs with a case fatality rate close to 100%. The virus continues to spread globally and it poses a real threat to the U.S.A swine industry. There is no vaccine or treatment available and therefore, it is imperative that safe and efficacious vaccines are developed to safeguard the swine industry. In this study, two vaccine candidates, namely B119L and B646L, were selected for development of a prototype subunit vaccine based on chaperon-mediated enhancement of target antigen expression. The B119L antigen was selected because it is critical for virus assembly, is a highly immunogenic antigen, and it is also a highly conserved protein amongst all ASFV isolates studied to-date. The B646L antigen, the conserved major capsid protein, was selected since it induces antibodies capable of inhibiting binding of the ASF virus to permissive cells and it has been shown to induce lymphocytes that are capable of killing swine cells infected with the ASF virus. Two additional ASFV proteins, A151R which is a natural chaperone for B119L and B602L which is a natural chaperone for B646L, were also selected. We used synthetic genes to generate replication-incompetent recombinant adenoviruses expressing the A151R, B119L, B602L, and the B646L antigens and the authenticity of the antigens was validated using convalescent ASFV-specific swine serum. Immunization of commercial piglets with a cocktail containing the recombinant adenoviruses primed strong ASFV antigen-specific IgG responses that underwent rapid recall upon boost with the priming cocktail and dose. Notably, most vaccinees mounted robust and significant IgG responses against all the antigens in the cocktail. Most importantly and relevant to vaccine development, the induced antibodies strongly recognized the actual ASF viral proteins and ASFV-infected cells. The recombinant adenovirus cocktail also induced ASFV-specific IFN-γ-secreting cells that were recalled upon boosting. Evaluation of local and systemic effects of the recombinant adenovirus cocktail post-priming and post-boosting showed that, the prototype vaccine was well tolerated and no serious negative effects were observed. Taken together, these outcomes showed that the adenovirus-vectored ASFV multi-antigen vaccine cocktail was capable of safely inducing strong antibody and IFN-γ+ cell responses in commercial piglets. These results support use of the replication-incompetent adenovirus as a vector for the development of a commercial vaccine for protection of commercial pigs against African swine fever virus.