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Short Commentary

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Control of Foot-and-Mouth Disease When Vaccines are Not Available

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Commentary

Vaccination and depopulation are the methods for control of Foot-and-Mouth Disease (FMD). Another tool is needed to manage FMD Virus (FMDV) if sero-type vaccines are unavailable. The USDA plans to vaccinate cattle if there is a major FMDV outbreak in the USA, but this plan is hampered by the lack of a stockpile of FMDV vaccines to treat millions of animals in a timely fashion. In the absence of FMDV specific vaccines strategies to induce or administer interferon (IFN) might limit FMDV replication and disease in cattle and swine. A group of USDA Animal Research Service (ARS) scientists have reported that the FMDV establishes infection in susceptible cells/hosts by its ability to subvert key host defenses, specifically the inducible IFN response. FMDV inhibits production of IFN alpha (α) [l] and blocks a key IFN-inducible, antiviral pathway, i.e.- Double-Stranded RNA (dsRNA) - dependent Protein Kinase R (PKR) [2]. Moreover, FMD Virion Protein 1 (VP1) has been specifically identified as a viral-origin IFN suppressor molecule by interacting with soluble resistance-related calcium protein sorcin [3]. Since a key FMDV control method by host cells is suppression of IFNα production by FMDV-infected cells then exogenous treatment with IFNα or induction of endogenous IFN should help control FMD. Indeed, this vulnerability of FMDV to IFN has led to a novel viral disease control strategy using recombinant replication-defective human adenovirus 5 vector containing various species IFN genes. Results varied by species.

ARS scientists reported that a human adenovirus type 5 vector containing porcine IFNα (Ad5-plFNα) injected into swine induced IFN production in these swine and completely protected them from FMD when challenged with virulent FMDV [4]. These swine remained FMD-asymptomatic, did not develop viremia nor did serum contain antibodies against viral nonstructural FMDV proteins. ARS scientists reported that Ad5-pIFNα given to pigs 1 to 5 but not 7 days prior to challenge with virulent FMDV were completely protected from FMD-disease. Pigs were protected even two days after IFN was no longer detected in the blood, likely because of the induction of IFN stimulated genes (ISG) [5,6]. This same research group reported that intramuscular (IM) injection of Ad5pIFNα protected swine against multiple serotypes of FMDV. IM inoculation of a 10-fold lower dose of Ad5-pIFNα at four sites in the neck compared with one site in the hind leg protected swine against FMDV challenge [7].

A fusion protein of porcine IFN regulatory factors (IRF) 7 and 3 delivered by an adenovirus vector [ad5-poIRF7/3(5D)] is an effective treatment to prevent FMD in swine. Animal pretreated with ad5-poIRF7/3(5D) 1 day before being exposed to FMDV and were completely protected from viral replication and clinical disease [8]. The doses of ad5-poIRF7/3(5D) required for protection were lower than those previously reported for similar approaches using Ad5 vectors delivering type I, II, or III IFN.

When the Ad5-pIFNα vectored porcine IFN delivery system was injected into cattle, Ad5-pIFNα, provided partial *in vivo* protection by delaying viremia for one day and decreasing vesicle formulation [5] in challenged cattle. Subsequently, the ARS identified bovine IFN lambda-3 (boIFN-λ3) and demonstrated that expression of this molecule using recombinant replication-defective human Ad5 vector, Ad5boIFN-λ3 exhibited FMDV-antiviral activity *in vitro* and *in vivo*. Inoculation of cattle with Ad5-boIFN λ3 induced systemic antiviral activity and up-regulation of ISG expression in the upper respiratory airways and the skin. ARS demonstrated that FMD disease could be delayed for at least 6 days when cattle were inoculated with Ad5-boIFN λ3 and challenged one day later with virulent FMDV.

The delay in the appearance of disease was significantly prolonged when treated cattle were challenged by aerosol of FMDV; clinical signs of FMD-disease, viremia, or viral shedding in nasal swabs were not observed in Ad5-boIFN-λ3-treated cattle for at least nine days after challenge [9].

Murine knock out models confirm the importance of the ISG IP-10 for FMDV resistance. Mice were screened for 86 genes and significant up-regulation was reported in 36 of the 86 genes at 3, 6 and/or 24 hours. The ISG IP-10 was up-regulated greater in mice than any other gene. The authors acquired IP-10 knockout mice and showed that only 30% of knockout mice survived FMD compared to 100% survival of mice with IP-10 intact [10]. FMDV inhibition *in vivo* by IFN has been known for 40 years. IFN-induced in the nasal secretions (NS) of cattle by Infectious Bovine Rhinotracheitis (IBR) virus given intranasally provided protection against FMDV challenge [11]. One or 2 days after intranasal vaccination with IBR virus, calves were challenged with FMDV. IFN was detected in the NS within 24 hours and for 10 days after IBR virus inoculation. Vaccinated calves had a milder course of FMD and greater than a 99% reduction in NS FMDV.

Vaccines, Induction of the IFN Response and Protection Against FMDV

When studying FMDV transmission from carrier to susceptible cattle, carriers of FMDV were inoculated intranasally with IBR virus to create a stress which might increase excretion of FMDV from carrier cattle. However, FMDV was not detected in esophageal-pharyngeal fluid of the 2 carrier animals a day after IBR virus inoculation and was not detected again during the 4-week sampling period [12]. IFN is induced in the NS of feedlot calves by modified live intranasal IBR viral vaccine [13,14]. Cattle given Coital Vesicular Exanthema Virus (CVEV) before inoculation with FMDV developed a milder form of FMD and developed FMD later than control calves [15]. The induction of IFN by the CVEV was perhaps responsible for the protection noted. If specific FMDV vaccine is not available, modified live IBR viral vaccines (already USDA-approved for cattle use) can be given to induce IFN to possibly help animals limit the severity of FMD.

Another animal viral vaccine in the USA that can induce intranasal IFN is a bluetongue virus (BTV) vaccine USDA-approved for sheep. A safety study of sheep BTV vaccine was conducted in cattle [16]. Given intranasally, the BTV vaccine was safe and induced small concentrations of NS IFN. Swine were not given either IBR virus or BTV vaccines, but an inexpensive study would ascertain the safety and efficacy of either vaccine in pigs challenged with FMDV.

Viral inducers of IFN in cattle with FMD agrees with the successful use of oral synthetic IFN inducers which protected mice from a subsequent infection with FMDV. Richmond and Campbell reported that an oral IFN inducer protected mice when given 2, 24 or 48 hours before FMDV inoculation and another inducer protected mice when given 18 hours before FMDV [17]. A single injection into mice of 150 µg of the synthetic IFN inducer polyriboinosinic polyribocytidylic acid (PolyI: C) 18 hours before a challenge with 100 LD50 of FMDV was 100% protective [18]. PolyI: C is too toxic in cattle to be used in the control of FMD [19-21] but in pigs, PolyI: C was excellent in helping protect against FMD [22,23]. Various concentrations of PolyI: C were given intravenously to 11 calves (0.25 - 4 mg/kg weight) and 13 goats (1-4 mg/kg). It appears, except in pigs, the chemical inducers of lFN are too toxic to be useful in the management of FMD. This is in contrast to the control of FMDV reported from viral inducers of IFN or the administration of the IFN gene to livestock [24,25].

The oral delivery to animals of natural human IFNα (HuIFNα), we believe, has not been tested in FMD. However, oral delivery of HuIFNα is reported to be safe and efficacious in cattle with shipping fever or challenged with virulent IBR virus or *Theileria parva* [26-29]. Since the use of low-dose HuIFNα cost only pennies per dose, is easy-to-administer and has proven useful in other livestock diseases, it seems reasonable to test oral HuIFNα in FMD. In a study of 7,000 feeder cattle, a single dose of orally administered HuIFNα (0.7 International Units [IU]/kg body weight [BW]) at the time of diagnosis of respiratory disease, given with antibiotics, reduced mortality significantly ($p<0.001$), when compared to feeder calves given placebo and antibiotics [27]. When calves were given HuIFNα at 0.0, 0.05, 0.5 or 5.0 IU/kg bw for 4 consecutive days, starting 2 days before a virulent IBR virus challenge, those calves given 0.05 IU/kg bw had significantly ($P<0.05$) greater weight gain after 25 days and fewer days of fever (> 40°C) [27]. In studies of naturally occurring shipping fever, oral HuIFNα given for 3 days before shipping, or once after arrival, improved weight gain or reduced illness [28]. In a study of calves challenged with *Theileria parva,* the causative agent of East Coast Fever, some calves given oral HuIFNα survived an otherwise fatal challenge [29].

Does IFNα given orally modulate expression of ISG *in vivo*? It has been reported that injected IFNα or IFNα given orally up-regulates Mx (a type I IFN specific induced protein) in mice and humans [30], 2'5' adenylate synthetase in mice and guinea pigs [31-33] and other genes in humans [33] and mice [34,35]. ISG are up-regulated within a few hours after oral IFNα administration [36,37]. A 15kDa protein (ISG-15) is up-regulated in human buccal epithelial cells *in vivo* and *in vitro* with a peak level of ISG-15 detected 2 hours after oral HuIFNα administration [35]. Up-regulation of Mx proteins was detected in the spleen of mice, and in the peripheral blood mononuclear cells of humans, 2-4 hours after murine IFNα or HuIFNα, respectively, were ingested [30]. These data demonstrate that orally administered lFNα has rapid and systemic biological effects in animals and humans.

The testing of orally administered IFNα to help control FMDV in an emergency is recommended. The IFNs are widely available in purified form as both naturally occurring and as recombinant molecules. An important facet of the lFNs is the fact that the

IFNα family is not species-specific in action. Cells of human origin are protected by IFN from animal origin and animal cells are protected by IFN of human origin. Bovine IFN is active on primate [38,39], porcine [40] and human cell cultures [40]. Porcine IFN is active in human cells [41]. Human IFNα is active on porcine [42], bovine [42-45], and feline [46] cells. Within 8 hours, 50 and 200 units of oral bovine IFNα induced significant ($P < 0.05$) changes in expression of 41 of 92 tested autoimmune and inflammatory response-associated genes. These data suggest that orally administered IFNα in cattle provided short-term antiviral immunity [47].

Testing will probably show that IFNα (in rations or water) will supplement production of endogenous IFN resulting in significant protection against FMDV. The US government has maintained a FMD free status since the last outbreak of FMD in 1929. The last outbreak in Canada was 1952 and in Mexico in 1954. It has now been more than 60 years since FMD occurred in North America. The problem facing the government and the livestock industry is how to deal with FMDV if it is introduced on purpose. When a small outbreak of FMD occurs, USDA, APHIS plans to stop all animal transportation, slaughter and dispose of infected and exposed animals, and to clean and disinfect premises in contact with infected animals. The plans of APHIS will successfully eliminate FMD if it is accidentally introduced into a single location in the US.

However, if someone repeatedly introduces one or more serotypes of FMDV at multiple sites, the eradication plans of APHIS cannot succeed. At some point the cost of eradication will exceed the benefit of eradication. Too many of the 97 million cattle and 60 million hogs will be killed in an attempt to eradicate FMDV repeatedly introduced. Someone may force the US livestock industry to live with FMDV. Vaccination and immunomodulation using IFN are the tools that may help the livestock industry survive FMD..

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