ARS ATA Workshop, April 2016
Ames, Iowa
Swine Working Group

The working group outlined strategies aimed at prioritizing research for work related to alternatives to antibiotics (ATA) for swine, particularly in light of FDA regulations set to go into effect in January of 2017. A first initiative outlined by the group included identifying swine diseases that are currently controlled with the use of medically-important antibiotics. These microbes would then be prioritized for research initiatives to identify an alternative for treatment and/or control. It was also noted that basic research on bacterial pathogens was important for identifying drug and/or vaccine targets (Table 1).

There was extensive discussion on the types of products already marketed to swine producers as methods to improve health, or serve as an ATA. The swine-working group had two representatives from the National Pork Board (NPB) that participated in discussions, and they noted that a recent initiative from the NPB included a working group to identify non-antibiotic interventions documented to be used in swine. The document included a technical merit score, which was a semi-quantitative measure of efficacy of specific approaches. In light of the NPB generated table, and discussions amongst the group, the types of alternatives for consideration with a research priority are indicated in Table 2.

The group commented on the large number of non-vaccine ATAs currently marketed to producers for particular conditions, but without an identified mechanism of action for the particular product. The group concluded that there is value in investigating promising products to identify mechanisms of action, and attempting to understand why a product may provide benefit on some farms but not others. There was also interest in methods to integrate products with a noted benefit into the different production stages, or identifying reasons why the product has limited efficacy throughout all stages. For example, acidifiers and immunoglobulin-based approaches have been shown to be efficacious in some instances, but only at certain stages of production. There was interest in research initiatives aimed at implementing these types of products throughout the production cycle.

There was enthusiasm for exploration of new approaches to serve as ATAs, including immunomodulators and host-derived proteins. But there was also concern for the potential cost of such approaches, and specificity. Prebiotics and probiotics were also discussed, as methods to potentially modulate the microbiota for production and prophylaxis. It was noted that data on the ability to modulate the microbiota of the pig at different stages of production was minimal, and that basic research was needed to better understand the interaction between the microbiome and health of the animal to determine

if this approach may be of benefit. The need for research was noted for both the intestinal and respiratory tract microbiota.

For all ATA studies working on efficacy and/or mechanisms of action, data should be made available to producers and researchers. The data should include specific conditions (housing, other infectious agents in the animal, age, breed) in which the ATAs were shown to be effective. Efficacy studies should include evaluation in production conditions (not only BSL2 research barns), with a clear indication of the infection and immune status of the animals under test. This will help determine if a product works only in specific cases and minimize the conflicting results on efficacy of ATAs currently used in swine production.

Along with identifying mechanisms of action and specific conditions in which ATAs have efficacy, a clear set of parameters to be measured and evaluated during any ATA efficacy testing need to be identified. A consortium of researchers, practitioners, producers, and industry partners could set these guidelines, perhaps with participation from stakeholder representatives, such as the National Pork Board. These guidelines would establish specific quantitative measures required for each study, as well as metadata to capture for reporting results.

Table 1: Alternative strategies for combatting diseases in swine in which medically-important antibiotics are used

	Primary Agent (disease)	Antibiotic Use	Current commercial non-antibiotic product available	Alternative Biocompound	Major limitations/constraints to development or implementation	Priority given non-antibiotic alternative/limitations
Enteric (weaners or finishers)	*Escherichia coli*	High	Vaccine, passive immunoglobulin (plasma or egg IgY)	Vaccine	timing of vaccination, maternal immunity	High
				Immunoglobulin; IgY, IgG	production costs; IgY specificity; stability	
				bacteriophage	transient; development of phage-resistance	
				lysins/antimicrobial peptides	manufacturing cost	
				Prebiotics/Probiotics	success is dependent on environmental/husbandry conditions	
				Organic acids/diet acidifiers	application timing, efficacy	
				Dietary Zinc/Copper	Environmental concerns; long term (>4 weeks) can detrimentally effect growth	
				Genetic resistance - ETEC receptor deficient pigs	not effective against all strains	
	Lawsonia intracellularis	Med	Vaccine	Vaccine	timing of vaccination, application methods	Medium
	Brachyspira hyodysenteriae	High	No	Vaccines	immunogenicity, cross-protection against different serotypes	Medium
				Dietary Zinc/Copper	Environmental concerns; long term (>4 weeks) can detrimentally effect growth, administration timing	
				Prebiotics/Probiotics	success is dependent on environmental/husbandry conditions	
				Dietary manipulation	basic research on microbiota, contribution of grain/fiber types to disease	
Respiratory & Systemic Disease	*Mycoplasma hyopneumoniae*	High	vaccine	Vaccines	Limited efficacy, interference by maternal immunity	Medium
	Pasteurella multocida	High	Vaccine for atrophic rhinitis but not pneumonia	Vaccines	immunogenicity, protection against pnueumonia	Medium
				Immunomodulators	immune targets, delivery, efficacy without side effects	
				microbiota manipulation	lack of basic information on respiratory tract microbiota, identification of commensal to compete	
	Streptococcus suis	High	vaccines (mainly autogenous), husbandry practices to protect neonates	Vaccines	High genetic/antigenic diversity thus limited cross-protective efficacy, interference by maternal immunity	High
				Immunomodulators	immune targets, delivery, efficacy without side effects	Medium
				microbiota manipulation	lack of basic information on respiratory tract microbiota, identification of differences between virulent and commesal strains	
	Haemophilus parasuis	High	vaccines (mainly autogenous)	Vaccines	High genetic/antigenic diversity thus limited cross-protective efficacy, interference by maternal immunity	High
				Immunomodulators	immune targets, delivery, efficacy without side effects	Medium
				microbiota manipulation	lack of basic information on respiratory tract microbiota, identification of differences between virulent and commesal strains	
Foodborne Agents	Salmonella spp	Low	Vaccine	bacteriophage	practical administration modes; development of resistant bacteria; induction of endotoxin release by bacteria (i.e. safety issue); regulatory approval	Low
				lysins	administration stability; manufacturing costs	
				antimicrobial peptides	pharmacokinetics of AMPs in vivo is lacking; narrow antibacterial spectrum	
				Prebiotics/Probiotics	variable successfulness; prebiotics may increase satiety and subsequently decrease feed intake and weight gain	
				essential oils	effectiveness observed in vitro; poor efficacy in pigs may be due to essential oil absorption in pig stomach, reducing availability to reduce Salmonella in intestines	
				Immunomodulators	manufacturing cost; therapy does not directly kill/inhibit microorganism	
				Other: acidified water and feed such as butyrate-coated micro-beads	Efficacy not always documented	
Growth Promotion	N/A	High	N/A	microbiota manipulation	need for basic research to understand mechanism, metabolism, microbiota, immune changes	High

Table 2: Types of alternatives for swine and research priority sc

Type of Alternative	Example	Research Priority
Immunomodulators	Cytokines / chemokines / host immune proteins	Medium
	Innate defense molecules	Medium
	Vaccines	
	Antigen Delivery Systems	High
	Adjuvants	Medium
	Immunglobulins	High
Bactericidal Agents	Bacteriophages	Low
	Antibacterial lytic enzymes	Medium
	Inorganic metals	Medium
Nutrients	Prebiotics / probiotics	High
	Organic acids	High
	Essential oils	Low
	Phytochemicals	Medium
Other	Microbiome modulation	High
	Genetic testing/selection/modification	Medium