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Host-targeted approaches to managing animal health: old problems and new tools

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ABSTRACT

Our fellow medical and regulatory scientists question the animal producer's dependence on antibiotics and antimicrobial chemicals in the production of animal products. Retail distributors and consumers are putting even more pressure on the animal industry to find new ways to produce meat without antibiotics and chemicals. In addition, federal funding agencies are increasingly pressuring researchers to conduct science that has application. In the review that follows, we outline our approach to finding novel ways to improve animal performance and health. We use a strict set of guidelines in our applied research as follows: (1) Does the work have value to society? (2) Does our team have the skills to innovate in the field? (3) Is the product we produce commercially cost-effective? (4) Are there any reasons why the general consumer will reject the technology? (5) Is it safe for the animal, consumer, and the environment? Within this framework, we describe 4 areas of research that have produced useful products, areas that we hope other scientists will likewise explore and innovate such as (1) methods to detect infection in herds and flocks, (2) methods to control systemic and mucosal inflammation, (3) improvements to intestinal barrier function, and (4) methods to strategically potentiate immune defense. We recognize that others are working in these areas, using different strategies, but believe our examples will illustrate the vast opportunity for research and innovation in a world without antibiotics. Animal scientists have been given a new challenge that may help shape the future of both animal and human medicine.

1. Changes in antibiotic policy in the United States

The US Food and Drug Administration (FDA) has provided guidance regarding the use of antibiotics deemed as medically important in animal feeds (FDA Guidance 209, 213, and Veterinary Feed Directive) [1]. In these US guidelines (mandatory after voluntary changes have been made), medically important antibiotics should no longer be used for the purpose of improving animal growth and feed efficiency, and when medically important drugs are used, their use should be under the care of a licensed veterinarian. Medically important drugs that have been sold "over the counter" will now be sold under a "Veterinarian Feed Directive Status." FDA Guidance for Industry 3152 Appendix A lists antimicrobials that are considered important to human medicine (eg, penicillins, cephalosporins, carbapenem, quinolones, fluoroquinolones, aminoglycosides, macrolides, tetracyclines, and glycopeptides) [2]. Ionophores and bacitracin, both considered antibiotics, and the latter used in human medicine, are not included in the guidance.

Consumer expectation for antibiotic-free products exceeds FDA regulations. USDA does not approve claims for "antibiotic free" but will accept claims for "no antibiotics administered" or "raised without antibiotics." In the United States, poultry-fed ionophores for the prevention of

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coccidiosis cannot be used with products labeled as “raised without antibiotics” because ionophores are antibiotics. New US policies and regulations, as well as pressure from consumer groups and food service providers, have placed demands on scientists to find alternatives for antibiotics in the United States. Ideas will likely come from developments in the European Union, where strict policies on antibiotic use have been operational for more than a decade, and some will be the result of continued discovery around the globe. In some cases, the industry may be reluctant to accept new approaches for concern about animal welfare and human health [3].

2. Historical perspectives on antibiotic use in agriculture. A guide for moving forward

The value of antibiotics as growth stimulants in poultry occurred nearly simultaneously with their discovery as therapeutics in the treatment of disease [4]. Early studies showed that chick growth in germ-free environments was not stimulated with antibiotic use; however, germ-free chicks had growth rates and feed efficiency 10% to 15% greater than those grown in a conventional environment [5]. The use of antibiotics partially restored slower weight gains associated with microbial colonization of the gastrointestinal tract [6] by a mechanism proposed by Cook [4]. Sanitation, subclinical disease, and vaccination also prevented animals from performing to their genetic potential. Losses were also minimized through the use of antibiotics [7]. Even though microbial resistance was linked to antibiotic use beginning in the 1940s, resistance was managed within the animal agriculture sectors. Evidence that growth-stimulating effects of antibiotics did not diminish over many years of use [8–10] argued against resistance concerns. Indeed, penicillin continues to markedly improve broiler growth even today (+17%) [11].

For many years, there was a lack of evidence to support a ban of antibiotic use in animal production. However, sound science on the potential of spreading antibiotic resistant microorganisms from animals to humans appeared in 1986 [12]. In this study, researchers followed the movement of a resistance plasmid to a newly introduced antibiotic in swine diets. After 2 yr of using noureseothricin in swine diets, 33%, 18%, 17%, and 16% of the *Escherichia coli* isolates from pigs, pig farm employees, family members of pig farm employees, and outpatients from the village, respectively, had noureseothricin resistant *E coli*. Noureseothricin-resistant microbes were not found in regions where the antibiotic was not used. Witte [13] also describes that the resistant plasmid was also found in *Shigella* (a human pathogen). Witte’s conclusion was that antibiotics as growth promoters should be phased out and scientists needed to develop alternatives to antibiotics for agricultural uses.

During the 2000s, research in Europe was showing clear links between the use of antibiotic in animal agriculture and resistant organisms in pig farmers. Rinsky et al [14] conducted a study in the United States to estimate the contribution of antibiotics used in farmed pigs and poultry on the presence of methicillin and multi-drug resistant *Staphylococcus aureus* (MRSA and MDRSA, respectively). In their study, farmers and family members were placed into 2 groups, those working on farms using antibiotics and those working on farms where antibiotics were not used. The incidence of MRSA in the farm workers was similar in the 2 farm groups, 32% of the farm workers from the antibiotic use farms had MDRSA, whereas 22.9% from the antibiotic free farms had MDRSA. However, household members of farmers working on antibiotic use farms had 28.6% MDRSA, whereas none had resistant strains when household members were associated with farmers that worked on an antibiotic free farm. Tetracycline-resistant *S aureus* was increased nearly 20-fold in farmers on antibiotic use farms compared with farmers on nonuse farms. Although agricultural use of antibiotics has received increased scrutiny in recent years, there is no question that the over-prescribed use of antibiotics, and perhaps biocides (not alcohols), directly used by humans, is also having major impact on conserving the long-term usefulness of antibiotics [15–17]. However, the human antibiotics and the resultant increase in antibiotic resistance does not diminish the responsibility of animal scientists to pursue new alternatives to antimicrobial use in animal agriculture. The last decade has resulted in a number of new products and strategies to reduce antimicrobial use. Animal scientists must continue to explore novel technologies that advance both animal and human health.

3. Host targeting. A strategy to reduce antimicrobial use in animals and humans

Antibiotics and other antimicrobials have been effective in improving the efficiency of animal production and health by directly targeting pathogens. When therapeutic approaches were not available or effective (ie, viruses), vaccination was a means of generating immunity to control infection. The loss of certain antibiotics due to new FDA policies in the United States and the increasing demand for antibiotic free animal protein has increasingly put pressure on animal producers to find new approaches to maintain animal health and efficient production systems without the use of antimicrobials. Vaccination has limitations in that, depending on the vaccine, vaccination can negatively impact animal performance and in some cases have delivery limitations [4,17,18]. Animal industries need scientists to discover new technologies and strategies for assuring the health of animals.

In the last 2 decades, scientists have been effective in bringing forth those new products, and the use of these new products has been widely accepted and expanded. The use of pre- and pro-biotics for the exclusion of infecting pathogens is now commonplace in animal production units. Enzymes have played beneficial roles in improving nutrient digestion and favoring a healthy intestinal microbiota. Feed acids and essential oils, as well as microbial and plant products, have been identified as useful for controlling pathogens and improving feed efficiency.

Increasingly there is interest in moving toward host-targeted approaches as a means of enhancing efficient animal meat production and health [7]. Table 1 lists research areas that our laboratory has been exploring in an attempt to improve animal health and efficient meat production. Our targets include infection detection measuring host