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Allied Industry Approaches to Alter Intramuscular Fat Content and Composition in Beef Animals

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Abstract

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Keywords

adipocytes, meat quality, review

Disciplines

Agriculture | Animal Sciences | Meat Science

Comments

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ABSTRACT: Biochemical and biophysical research tools are used to define the developmental dynamics of numerous cell lineages from a variety of tissues relevant to meat quality. With respect to the adipose cell lineage, much of our present understanding of adipogenesis and lipid metabolism was initially determined through the use of these methods, even though the *in vitro* or molecular environments are far removed from the tissues of meat animals. This concise review focuses on recent cellular and molecular biology-related research with adipocytes, and how the research might be extended to the endpoint of altering red meat quality. Moreover, economic and policy impacts of such in animal production regimens is discussed. These issues are important, not only with respect to palatability, but also to offer enhanced health benefits to the consumer by altering content of bioactive components in adipocytes.

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Introduction

A balanced diet should contain safe red meat products (Sofos 2008; Vandendriessche 2008), as lean meat provides a variety of nutrients required for a healthy lifestyle (Schönfeldt and Gibson 2008; Wood and others 2008). However, the fat (adipose tissue) component of red meat still draws negative attention (Web and O'Neill 2008; Wood and others 2008). Despite the positive contribution of adipose tissue to the appearance, texture, flavor, firmness, caloric value, and shelf-life of red meat products (Dransfield 2008; Ngapo and Garipey 2008; Web and O'Neill 2008; Wood and others 2008), excess adipose tissue (Wood and others 2008), and meat products containing saturated fatty acids (Wood and others 2008) are considered unhealthy (Schönfeldt and Gibson 2008; Web and O'Neill 2008; Hausman and others 2009).

It is apparent that scientists have become increasingly effective in their *in vitro* identification of potential regulatory agents that could significantly impact the adiposity of red meat animals (Mersmann 1998a; Hausman and others 2008b, 2009). Studies using cellular methods have documented regulators of adipocyte cell cycle transition (Hausman and others 2008b, 2009), toxins (Hausman and others 2008b), cellular and molecular markers of adipogenesis and lipid metabolism (Kokta and others 2004; Fernyhough and others 2007; Hausman and others 2008b), metabolic modifiers

(Hausman 1989; Peterla and Scanes 1990; Mersmann 1998b; Gondret and others 2008; Hausman and others 2008b, 2009), and potential secretion of endocrine and paracrine regulators that might regulate a variety of different tissues *in vivo* (Jacobi and others 2006; Gabler and Spurlock 2008; Hausman and others 2008b). Molecular methods have yielded a variety of linkages between specific genes and numerous meat quality characteristics such as fatness (Oishi and others 2000; Dekkers 2004; Michal and others 2006; Sasaki and others 2006; Hausman and others 2007, 2008b, 2009; Hollung and others 2007; Lee and others 2007; Taniguchi and others 2008a, 2008b, 2008c). The question remains though, should bench scientists identify a viable marbling agent that modifies cellular signaling sufficiently to alter fatness of a meat animal, would the public ever see the results applied to meat production?

Red meat animal producers in the United States are not allowed to treat animals destined for human consumption with chemical agents that are deemed unsafe, except in the need of clinical intervention. Rompum (Xylazine), for example, is a carcinogen that is commonly used in clinical conditions, even in "organic" cattle. Moreover, a lengthy testing/review process is involved prior to the approval of any compound to enhance production (FDA 2006). More rigorous regulations (to the point of complete restriction) are in effect elsewhere in the world and will potentially become more prohibitive (Verbeke and others 1999; Higgs 2000; Higgins 2004; Crony and Millman 2007; Thompson and others 2007). At the same time, a proportion of consumers, producers, and scientists have voiced their belief that meat from animals treated with pharmaceuticals or fed feed treated with pesticides is less "healthy" to eat. In this environment, then, will any knowledge gained by cellular or molecular experimentation be applicable for the modulation of any aspect of meat quality? For example, if the research goal of a cellular or molecular meat scientist is to optimize adipocyte growth and development in specific adipose depots of red meat animals, how does one apply research observations to an effective (and acceptable) endpoint to alter red meat quality in the whole animal? Will whole animal production alterations be the only accepted method to attempt to manipulate such processes (Mir and others 2008)? The focus of this concise review is to demonstrate

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endpoints of such research efforts and to extend our previous review (Hausman and others 2009).

Intramuscular fat

At the cellular level, fattening of meat animals is a function of adipocyte size and numbers (Hood and Allen 1973; Robelin 1981; Hood 1982; Cianzio and others 1985; Gondret and Lebret 2002; Yang and others 2006) and distribution throughout the animal in a depot-specific manner (Hausman and others 2009) or in a specific muscle (Gondret and Lebret 2002; Albrecht and others 2006; Yang and others 2006). A recent review thoroughly discusses aspects of adipogenesis and lipid metabolism (Hausman and others 2009).

Meat tenderness and marbling endpoint

Marbling (intramuscular adipose tissue) has been shown to play an important role in the eating quality and composition of meat (Moloney and others 2001). While marbling may impact components of tenderness its regulation varies tremendously both within and across breeds of cattle (Albrecht and others 2006) and swine (Hausman and others 2009) and is determined by a wide range of factors such as genetics, husbandry (time of weaning, nutrition, duration of grow-out, physical activity), and seasonal temperature variations. Importantly, it has already been shown that marbling can be positively or negatively affected by agents commonly administered to cattle to promote growth rate and feed conversion efficiency, such as implants and β -agonists (Brandt and others 1996; Gaylean 1997; Macken and others 2003; Silence 2004). For example, marbling effects have also been demonstrated for melanogestrol acetate, a progestin used to suppress estrus, when dosed in-feed to steroid implanted finishing heifers (Macken and others 2003). Thus, the multivariate nature of the marbling process is underscored by the numerous influencing factors that modulate it (Devitt and Wilton 2001; Hausman and others 2007, 2008a; Tchkoia and others 2007). Furthermore, while there may be the potential to identify strategies to specifically enhance marbling content, little is presently known as to how these regimens may alter subcutaneous or intermuscular fat.

Adipose tissue can have positive or negative economic impacts on both beef and pork carcasses. In the United States, marketing of beef is based on both USDA yield and quality grades with the highest value given to carcasses with high-quality grades (more intramuscular fat) and the lowest value to low yield grades (more subcutaneous and internal fat). In addition, the USDA yield grade also predicts the amount of intermuscular fat in the beef carcass. Savell and Cross (1988) suggested that a minimum threshold for intramuscular fat was approximately 3% for all livestock species to ensure an acceptable eating experience. The 2005 Natl. Beef Quality Audit reported the average U.S. beef carcass has a USDA yield grade of 2.9 and a quality grade of Select (Garcia and others 2008). Three Natl. Beef Quality Audits have characterized the U.S. beef population prior to 2005, and there has been very little fluctuation in average USDA yield and quality grades. The USDA yield grades reported were 3.2, 2.8, and 3.0 for 1991, 1995, and 2000, respectively (Lorenzen and others 1993; Boleman and others 1998; McKenna and others 2002). Smith and others (1987) reported a linear and hierarchical relationship between USDA quality grades in beef and eating quality of the longissimus muscle. Neely and others (1998) examined 3 different beef muscles and found that the USDA quality grade only affected consumer preference for top loin steaks and that the amount of intramuscular fat may only be affective in sorting beef cuts that contain the longissimus muscle. In contrast, pork is marketed in the United States based on the percentage lean and carcass weight. While pork carcass weight is influenced by adi-

pose tissue deposition, the main depot of concern is the subcutaneous depot. In fact, a study conducted on the U.S. pork revealed that boneless loin chops were almost devoid of intramuscular fat (Wright and others 2005). Unlike beef, research shows that marbling has very little effect on the eating quality of pork (Rincker and others 2008) and that consumers prefer the appearance of pork chops that are not heavily marbled (Brewer and others 2001).

The interface of the USDA and adipose tissue occurs in the area of marketing and regulatory programs. Specifically, the Agriculture Marketing Service is responsible for developing and implementing the USDA grades for beef and pork and reporting on livestock and meat prices. The USDA has developed pork carcass standards (USDA 1985) and beef quality and yield grades (USDA 1997) to segregate carcasses based on their expected meat yield and palatability.

“OMICS” with adipogenesis or lipogenesis

Contemporary molecular techniques, both existent and on the near horizon, offer multiple approaches to a more productive understanding of adipogenesis and lipid metabolism. Genomic analysis of quantitative trait loci (QTL) and single nucleotide polymorphism (SNP) quantify and explain the underlying basis of genetic variation in populations, directly improving selection strategies for fat associated traits. Transcriptomics (gene expression) studies improve understanding of the species-specific importance of metabolic pathways and help identify additional components of complex intracellular and extracellular regulatory networks. Proteomic analysis helps to explain posttranscriptional modulation and the resulting physiological regulation dynamics downstream of expression. Thus, OMICS-based research may suggest pharmaceutical or nutritional intervention and indirectly support selection decisions.

Pathway-based approaches to identify potential candidate genes associated with fat deposition and composition for improving meat quality. It is well known that many pathways are involved in regulation of fat deposition, such as the mitochondrial biogenesis complex, the long chain fatty acids uptake complex, the sauvagine/corticotropin-releasing factor/urotensin I family and related families, the lipogenesis/lipolysis enzymes, and even cholesterol homeostasis pathway (Daniels and others 2009; Jiang and others 2009). Using a Wagyu x Limousin F2 reference population, our studies have revealed that the corticotropin releasing hormone (CRH; Wibowo and others 2007), fatty acid binding protein 4 (FABP4; Michal and others 2006), stearoyl-CoA desaturase (SCD1; Jiang and others 2008), mitochondrial transcription factor A (TFAM; Jiang and others 2005), urocotin 3 (UCN3; Jiang and others 2006), and ubiquinol-cytochrome c reductase core protein I (UQCRC1; Kunej and others 2007) are associated with beef marbling scores.

Pathway analysis has also identified several candidate genes that are associated with fatty acid composition. For example, stearoyl-CoA desaturase (SCD1) is an iron-containing enzyme that catalyzes a rate-limiting step in the synthesis of unsaturated fatty acids (Miyazaki and Ntambi 2003). The principal product of SCD is oleic acid that is formed by the desaturation of stearic acid. The ratio of stearic acid to oleic acid has been implicated in the regulation of cell growth and differentiation through its effects on cell membrane fluidity and signal transduction. Taniguchi and others identified a nonsynonymous mutation in SCD1 of Japanese-Black cattle that was associated with the saturation level of fatty acids and fat melting temperature (Taniguchi and others 2004). Similarly, the same allele is associated with the saturation level in American Angus cattle. Recently, Jiang and others (2008) identified additional SCD1

alleles that were significantly associated with 6 fat deposition and fatty acid composition traits in skeletal muscle. In particular, high stearoyl-CoA desaturase activities/alleles were positively correlated with beef marbling scores and the amount of monounsaturated fatty acids and conjugated linoleic acid content, but were negatively correlated with the amount of saturated fatty acids. Furthermore, Zhang and others (2008) identified a nonsynonymous mutation in the thioesterase domain of fatty acid synthase, which was associated with decreased amounts of unsaturated fatty acids. Similarly, a nonsynonymous mutation in myostatin is also associated with reduced levels of saturated fatty acids. Therefore, these studies provide evidence that it is possible to produce beef with high marbling, high amounts of monounsaturated fatty acids, and conjugated linoleic acid content, but with low amounts of saturated fatty acids.

Although not a focal point of this article, it should be noted that similar studies have been conducted with pigs. For example, porcine adipose tissue is innervated by adrenergic nerve fibers (Hausman and Richardson 1987). Trans-synaptic viral tracing techniques have identified multisynaptic pathways that link adipose tissue depots to the brain in the pig and other species. Transcriptional profiling has also been used in pigs to determine subcutaneous adipose depot-specific pathways that respond to either fasting (Lkhagvadorj and others 2008), feed restriction (Lkhagvadorj and others 2006), or response to melanocyte-stimulating hormone (MSH) injection in prepubertal gilts. In response to MSH injection, 5070 genes in adipose tissue were differentially expressed. For example, lipoprotein lipase, fatty acid synthase, aconitase-1, acetyl CoA synthase, leptin, and heat shock protein 70.2 genes were down regulated, whereas angiopoietin-like 4, pyruvate dehydrogenase kinase 4 isoform 1, uncoupling protein 3, and insulin-like growth factor binding protein-3 were upregulated. These results demonstrated that stimulation of MC4R markedly and rapidly affected adipose tissue gene expression. Clearly, adjustment of the environment with subsequent change in sympathetic outflow to subcutaneous adipose tissue could be used to create the desired nature and timing of adipose tissue deposition in specific adipose depots.

The expression of mRNA for a number of regulatory and metabolic genes has been examined in adipose tissue from growing pigs but most of these studies typically have examined the expression of 1 to 2 genes at a single age. Recently, adipocyte cell lines isolated from different animals were used to demonstrate that adipogenesis is controlled by species-specific mechanisms. For example, beef-derived adipocytes showed different regulation pathways than murine adipocytes (Fernyhough and others 2007; Taniguchi and others 2008a, 2008b). Lipid-filled pig adipocytes physically extruded lipid from the cell before they started to proliferate, whereas beef-derived adipocytes, that symmetrically or asymmetrically divide into daughter cells, do not expel cellular lipid (Fernyhough and others 2005a, 2005b). Gene expression profiling of porcine adipocytes showed that triacylglycerol hydrolase (TGH) expression was differentiation-dependent in porcine primary adipocytes and that TGH played a role in fasting-induced lipolysis but not hormone-stimulated lipolysis (Zhang and others 2008).

Transcriptome analysis of fat deposition and composition of beef and pork meat. Depot-specific adipocytes may be influenced by many factors including feeding behavior, growth, metabolism, and the development of puberty through the secretion of leptin, several interleukins, and a number of other cytokines (Barb and others 2006; Jacobi and others 2006; Trayhurn and others 2006). Recent technological advances have made it feasible to analyze the complete set of RNA transcripts (gene expression

and alternative splicing) produced in a tissue/cell at a given time (Mortazavi and others 2008; Pan and others 2008). Microarray analysis of the bovine subcutaneous adipose depot revealed that hundreds of genes were differently expressed between animals with low and high backfat thicknesses (Taniguchi and others 2008c), which suggests that the molecular mechanisms may vary during adipose depot formation. Furthermore, many transcription factors, intracellular signaling factors, and other regulatory factors are involved in the differentiation and function of depot-specific adipocytes (Farmer 2006; Rosen and MacDougald 2006; Prestwich and MacDougald 2007; Taniguchi and others 2008c). However, studies of the influence of age, nutrition, and hormones on gene and protein expression in adipose tissue from red meat animals have been limited in regard to the number of genes and proteins examined and the consideration of depot variation or influence (Fernyhough and others 2007; Hausman and others 2009).

Gene expression/transcriptome profiling provides a dynamic link between the genome, the proteome, and the tissue/cellular phenotype (Basu and others 2009). This can lead to further insight into the complex interplay of gene expression events involved in the development of meat quality (Basu and others 2009). Furthermore, the application of a functional proteomics approach to the identification of proteins associated with fat deposition and composition in meat will contribute to a better understanding of the biological processes that control adipose development and ultimately affect meat quality (Basu and others 2009). Through the application of functional genomic and proteomics tools, we will gain insight into how genetic components regulate adipogenesis, how they respond to environmental changes, and whether these changes affect the fat deposition and composition in meat (Basu and others 2009). These discoveries should allow us to establish better management systems to ensure the delivery of an optimal meat product that meets the needs of the consumer.

Animal/human health industry

Recent advances in bovine genetics and cell biology, especially aspects of the biology of the bovine adipocyte, have provided many of the tools required for rational-based discovery programs for beef marbling agents (Fernyhough and others 2007; Hausman and others 2008a, 2008b). Discovery programs in human medicine, especially those for obesity and diabetes, have developed other useful technologies such as bioassays for the molecular pathways involved in lipid and fatty acid processing (Spiegelman and Flier 1996; Horton 2002; Horton and others 2002; Bergen and Mersmann 2005).

From a drug discovery perspective, altering marbling is a double-edged sword. On the one hand, the complex cellular and metabolic regulation offers numerous potential targets for intervention to improve marbling. On the other hand, the total systems physiological complexity suggests that targeting single factors may not be sufficient to favorably affect marbling. As such, pharmaceutical-based approaches targeting the adipocyte represent only 1 potential strategy for improving marbling in cattle; new diets (containing nutraceuticals, for example), genetics/breeding systems, vaccines, and (perhaps) virtual screening (as a drug discovery tool) could each offer alternative approaches (Kim and others 2003; Sellner and others 2007). These approaches may pose fewer barriers to commercialization, especially those related to food and environmental safety. Identifying a pharmaceutical agent that meets all of the criteria required for approval as a marbling agent will not be a trivial exercise.

Is there a market rationale for the use of marbling agents in beef production? Although not yet substantiated by a product,

the potential market opportunity for a marbling agent for use in beef cattle can be estimated on the basis of historical price spreads across meat grades (determined principally by marbling score). Based on historical averages, a marbling agent that increased the number of cattle graded as choice by only 5% could be worth tens of millions of dollars. Cattle represent the largest economic opportunity for a marbling agent, but other livestock species, including swine, sheep, and poultry represent potentially lucrative opportunities for active compounds, as current production practices for all livestock are generally antagonistic to the marbling process (Sillence 2004; Hausman and others 2008a). The potential value of a marbling agent in the market place is supported by a broad range of economic and demographic factors. Consider the bottom line first. The Select/Choice price spreads for the U.S. beef—a direct function of marbling—have ranged \$6 to 12/100 weight since 2000, averaging \$10/100 weight. Marketing programs such as Certified Angus Beef (CAB[®]), which is based on marbling scores of average Choice or higher, take advantage of this price spread.

The gap between the numbers of CAB[®] cattle produced in the United States compared with the market need has typically ranged from 17% to 19% (Garcia and others 2008). This translates, roughly, into an opportunity of about \$80/head for the producer. Assuming a 6:1 return, this could translate into a product that sells for >\$10/dose regimen. This would provide a substantial market opportunity by any standards. In 2008, however, price spreads declined in response to global economic conditions; this highlights a potential caveat for any product that promotes meat quality only.

Numerous other factors favor the potential marketability of a marbling agent for beef cattle. Breeding programs have selected for faster-growing and more energy-efficient animals at the cost of marbling and tenderness (Hausman and others 2008b). Modern husbandry practices, especially in countries such as the United States that use feedlots extensively, have reduced the grow-out period to <24 mo in order to save feed, labor and time; cattle are thus harvested prior to the late phase of fat deposition. In addition, since the 1980s, beef production has expanded rapidly in the southern hemisphere, including Brazil and Argentina, where grass fed production accounts for >90% of the animals harvested. These animals are generally less marbled than cattle raised in North America, most likely a function of not only genetics and diet, but also due to the increased physical activity required of animals raised on pasture. A marbling agent could reverse the impact of these trends on meat quality.

Another emerging factor is the expanding use of growth-promoting agents, especially the β -agonists, that has led to improvements in performance (feed conversion efficiency, average daily gain) but has also led to less marbled and less tender cuts of meat. These compounds act specifically by repartitioning energy away from fat and toward lean muscle accretion (Sillence 2004). Adoption of these agents has been driven recently by remarkable increases in the price of corn and other feedstuffs, which now account for over 70% of the cost of raising beef in the U.S. finishing lots. The tremendous economic advantage they provide is incentive for continued and expanded use of these products. An agent that reversed the effects that β -agonists have on marbling and tenderness, without negating the growth advantages, would likely be well received by the market.

Indirect evidence for the concept that marbling in cattle can be affected by exogenous agents has already been demonstrated, based on observations that controlling levels of vitamin D and retinoic acid in the diet can result in predictable changes in marbling, and that marbling generally correlates in some fashion with blood levels of these vitamins (Gorocica-Buenfil and others 2007a,

2007b). Correlations between marbling and homeostatic signaling molecules that can be targeted by drugs, such as leptin (Bonnet and others 2007; Cheong and others 2008) support the concept that selective marbling agents might be identified. In the target animal itself, the administration of melanogestrol acetate (MGA) in finishing heifers that are also implanted with anabolic steroids has been shown to promote marbling (Macken and others 2003). However, marbling is not affected by MGA in heifers when administered alone or in implanted or nonimplanted steers (Montgomery and others 1992; Brandt and others 1996; Hendricks and others 1997).

Adipocytes hold the potential for synthesizing or serving as depots for other health factors (conjugated linoleic acid, omega-3 fatty acids, and other health-promoting proteins and fatty acids). These could be introduced by way of adipocytes through genetics, diet, or pharmaceutical agents (Gillis and others 2004; Dhiman and others 2005; Noci and others 2005; Bouattour and others 2008). The concept of “healthy” beef would be appealing to many consumers, especially those already willing to pay a premium for omega-3 enriched poultry and fish products.

What would it take to discover and develop a beef-marbling agent? The strategy adopted will depend to some extent on whether the approach to improve marbling is pharmaceutical-, nutraceutical-, vaccine-, or genetics-based. Approaches to a pharmaceutical could consist of high throughput targeted screening against a key enzyme or receptor identified in basic studies that delineate lipogenesis and adipogenesis in cattle (Hausman and others 2008a, 2008b). Alternatively, candidate compounds could be selected from agonist families already identified by human pharmaceutical programs, such as those targeting diabetes or obesity, in which fat metabolism or deposition are key endpoints. In this case, the validity of the target, albeit in other species, would already be established by RNA interference studies and pharmacology (Sellner and others 2007). Ideally, the importance of the target would also be consistent with data from genetics studies in beef cattle suggesting a role for the target in intramuscular fat deposition (Kim and others 2003). With such background, *in vivo* proof-of-concept studies in cattle (for example, treatment of cattle with a peroxisome proliferator-activated receptor γ (PPAR γ) agonist or compounds already shown to promote lipogenesis) could be completed in a short timeframe. Testing these compounds could begin *in vitro* using a bovine adipocyte assay. This assay would be designed to determine if the compound drives the expression of key genes or activates key proteins in the adipocyte differentiation pathway (Fernyhough and others 2007), and to gain early insights into relative agonist activity. Early testing of these compounds for metabolic stability would also be done, using bovine liver tissue or hepatocytes. In general, compounds that are more stable to degradation would be favored over those that are rapidly degraded, especially at the early stages of concept testing. Compounds with lower stability compared with metabolic degradation may be desired for development, consistent with a short or zero-day withhold period, if drug or active metabolite residues are an important issue for the approach.

Candidate compounds that show adipogenic activity in the bovine adipocyte assay could be tested in a secondary screen or taken directly to cattle as the target species to define pharmacokinetics (time course of activity) and pharmacodynamics (effective concentrations or doses). These could be evaluated using marbling as the desired outcome or appropriate biomarkers within the target species. The biomarkers selected to evaluate drug activity could include metabolites immediately downstream from the target enzyme, perhaps measurable in a blood sample, or target

gene expression levels in intramuscular fat deposits obtained from skeletal muscle (Fernyhough and others 2007; Hausman and others 2008a, 2008b). These studies would be designed principally to test the concept that the drug is capable of driving intramuscular fat deposition in the right direction and, secondarily, to identify a safe dose for achieving that endpoint.

Once a chemical series is identified with activity in the target animal, additional screening would likely be required using the bovine adipocyte model on a large number of structural analogs against the target to optimize the lead for potency within the chemical family of the candidate compound. These studies would be coupled with information obtained from *in vitro* and *in vivo* metabolism studies toward identifying compounds that have suitable metabolic profiles (that is, short half-life or low tissue residues if the approach requires dosing late in the finishing phase).

Definitive proof of concept testing in finishing cattle would involve dosing finishing cattle, probably over several weeks initially, and testing for significant increases in marbling score and intramuscular fat levels using a defined cut of meat (for example, 11th rib eye) as well as other carcass quality indicators (% lean, shear force, pH). It would also include measurement of key biomarkers. Subsequent to establishing efficacy, target animal safety testing at 3× and 10× the projected use level for an injectable or an in-feed agent, respectively, would be done, along with preliminary formulation and large-scale production studies.

Postdiscovery drug development processes would not likely be unique for a marbling-enhancing product. In addition to multisite testing for potential influences of breed, husbandry practices, and potential interactions with other compounds typically used by the target market, extensive testing for production/formulation and safety, including target animal, human food, and environmental, would be required, as they are for any new compound that enters the food chain. Regional differences in regulatory requirements would clearly affect the development process, that is, performance agents are not currently approvable/marketable in the European Union.

What are the potential barriers to the successful discovery, development, and introduction of a meat quality product? Two general types of challenges would face such a product: barriers to discovery and development, and barriers to market acceptance. One barrier to discovery is the desired outcome. The link between marbling and tenderness is not high (Haley 2006). One implication of this is that an intervention that increases marbling may not achieve the desired outcome of also increasing tenderness. Raising caloric content without a corresponding increase in eating quality could well be counterproductive. Alternatively, lipid content, *per se*, is a very minor contributor to tenderness, so some component of adipogenesis could be an excellent surrogate as a screen for the physiology underlying improved tenderness. For example, the matrix protease MT1-MMP plays an important role in enabling adipogenesis (Chun and others 2006) and may reflect other protease activities influencing tenderness. An equally important scientific barrier to success is the current lack of a cost-effective surrogate model for efficiently testing early-stage concepts. Factors governing fatty acid processing in rodents, rabbits, pigs, and even goats differ substantially from cattle (Taniguchi and others 2008a). These differences point out the value of validating a specific response in lab animals as a surrogate for marbling. Species differences could also limit the ability to leverage active molecules across target animals (that is, activity of a marbling agent in cattle may not translate to swine). This would limit the market potential of a product.

Alternatives. Genetics and breeding programs could possibly circumvent or even work in concert with a marbling agent to reli-

ably produce cattle with high levels of marbling (Kim and others 2003; Taniguchi and others 2004; Haley 2006). With the advent of whole genome selection methodology it should soon be possible to account for a substantial proportion of the genetic variance associated with traits such as marbling. This would allow producers to dramatically increase selection intensity on traits such as marbling and thereby alter the product produced in subsequent generations. Whole genome selection strategies to improve traits of interest are cheaper and easier to implement than drug discovery, approval, and marketing. Furthermore, societal concerns associated with the use of pharmaceutical-based approaches do not apply to the selection of animals for enhanced traits of interest, which indicates that this approach could be readily accepted by society. Conversely, breeding programs could lead to the wide use of animals/breeds that are less responsive to certain treatments, including a marbling agent. It is already established that, for instance, fat deposition patterns and the adipogenic process vary across species (Allen 1976; Allen and others 1976), breeds of cattle (Kim and others 2003), and even at different sites within an animal (Hood and Allen 1973; Hood 1982). These types of genetic differences, along with differences in liver enzymes important to the metabolism of a drug, could affect the pharmacological response to a marbling agent, and add another layer of complexity and challenge to achieving a consistent response to a marbling agent. Furthermore, whole genome association studies should lead to a better understanding of the molecular mechanisms that control traits of interest. This should, in turn, generate new targets for pharmaceutical intervention.

Items to double-check. As noted above, economic incentives for improving growth rate and feed-conversion efficiency have favored the use of agents and husbandry practices that improve performance, often at the expense of marbling and tenderness. This trend will likely continue as feedstuffs, especially corn, become more expensive.

On the side of market acceptance, a broad range of logistical issues and consumer attitudes could limit the use of a marbling agent. Novel postharvest technologies designed to improve tenderness and flavor might circumvent the need. Although marbling score is a key parameter used today to value beef, tenderness, flavor, or alternative endpoints, including those potentially incorporated into “healthy” meat programs, may become more important in the future. The potential for this change in focus is exemplified by new marketing programs that target tenderness instead of marbling (Shackelford and others 2001).

There are no policy barriers in the United States that would, *a priori*, prevent approval of a promarbling or postmortem tenderness product, assuming target animal and human food-safety requirements are met. However, regional differences in regulatory environments (and requirements for approval) will persist for many years. One relevant consequence of this is that performance agents are not currently approvable in the European Union. This would likely prevent use of a marbling agent in those regions, and could restrict beef exports to those regions as well, both adversely affecting the market opportunity. It might be possible to address this issue by identifying agents that demonstrate health benefits to the animal in addition to the targeted effect on meat quality. Improvac[®] provides an example of this type of dual-action product. This immunological agent, directed against GnRF, leads to suppression of testosterone and thereby controls boar taint in male pigs. Its use circumvents the need for physical castration, allowing boars to be raised intact, and thus able to realize the health and performance benefits associated with its own natural androgens (Dunshiea and others 2001). Though it is impossible to predict the future direction of consumer attitudes toward any agent that enters

the food chain, it is reasonable to predict that public opinion will favor products that improve the health or welfare of the animal over those that do not.

Conclusions

1. Molecular biology techniques continue to demonstrate the nature and expanding function of the adipocyte. Based on recent history, these approaches and techniques will undoubtedly identify presently unknown functions of the adipocyte. Genome markers, probes, genome libraries, promoters, transcription factors of genes, and other tools for biological research and genetic improvement will result in the potential for generating genetically superior animals.

2. The use of molecular biological methods will reveal new insights into the physiology and regulation of marbling and its relationship to tenderness (quality) of red meats. Academics may argue the exact correlation, predictability, or shape of the curve, but this relationship remains at the core of the USDA quality grading system, and anyone who has participated in taste panels recognizes there is some relationship between marbling and meat tenderness. A more specific and detailed understanding of this relationship that will have direct implications for animal production and meat quality is within reach in the future.

3. Adipogenesis/metabolism culture systems will continue to be an important screening tool for identifying potential pharmacological agents. Beta agonists and PPAR agonists are examples of agents that alter adipose metabolism and/or proliferation discovered with *in vitro* screening, even though PPAR γ may not appear to be a good candidate gene marker for some red meat species. Moreover, other (mechanistic) knowledge from *in vitro* work will likely lead to refinement of further drug development or applications. Examples of these are less clear, but *in vitro* work has played a central role in the development of omega-3s or DHA as potential feed ingredients in an attempt to naturally bioengineer red meat to provide healthy supplements in the form of the right type of fatty acids.

4. The current market opportunity for a red meat marbling agent justifies investment in research in this area. Several convergent factors in the allied sciences, including advances in livestock genomics and metabolomics, knowledge around key biological processes in the bovine adipocyte, and the immense power of high throughput drug and vaccine screening systems, argue that the chances for technical success are improving for approaches targeting the adipocyte. Adipogenic compounds with the desired profile in cattle may already be contained within the compound libraries of pharmaceutical companies. Key challenges to reduce the science to useful marbling agents include the lack of knowledge about molecular targets fully validated in the target animal and potential issues around target animal and human food safety. Competing approaches, including advanced breeding techniques and postharvest strategies could circumvent the need for a marbling agent, as could a major shift in grading emphasis away from marbling (that is, toward tenderness). However, the potential economic benefits of a beef marbling agent that targets the adipocyte are probably sufficient to justify the risks posed by competing technologies and potential shifts in the market.

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