Excerpted from:

RECOMBINANT BOVINE SOMATOTROPIN FOR USE IN BEEF CATTLE

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Advances in technology and continual commercial application of this technology to animal agriculture has enabled producers to deliver large quantities of animal food products to the consuming public. The steady supply of these nutritious animal products has contributed significantly to enhancing the quality of life. Whereas in the early 1900's many of the health problems were related to nutritional deficiencies, today many of the health problems are associated with the over-consumption of calories, saturated fatty acids and cholesterol.

Whereas research in the past has focused primarily on methods to maximize productivity of food-producing animals to lower cost of production for the producer and cost of food products for the consumer, future research efforts will need to focus more on the development of technologies that will improve product quality and assure food safety. Recent advances in biotechnology such as the use of recombinant DNA technology to supply large quantities of polypeptide hormones such as somatotropin (ST) appear to hold considerable promise towards satisfying these changing demands for animal food products.

To ensure eventual consumer acceptance of these new technologies it will be critical to demonstrate that the technologies will: 1 - be cost effective, 2 - enhance nutritional value, 3 - improve product quality and 4 - be safe for human consumption, the target animals and the environment. Somatotropin is a polypeptide hormone secreted from the anterior pituitary that exerts control over numerous diverse metabolic processes. Although the exact modes of action for ST have yet to be fully elucidated, treatment of growing animals with ST has been shown to increase muscle growth and reduce adipose tissue stores. Somatotropin's actions on muscle growth are mediated indirectly via IGF-I to increase cellular proliferation and to increase whole-animal protein synthesis. The anabolic actions of ST on muscle and bone tissue, combined with the effects of ST on metabolism to redirect nutrient utilization, results in leaner tissue growth in meat animals.

RESEARCH DEVELOPMENTS LEADING TO USE OF RECOMBINANT ST

While the technology used to produce recombinant ST is relatively new, the research which led to the idea of using ST as an anabolic agent to enhance animal productivity is not. Studies conducted in the 1930s using crude preparations of pituitary ST in rats were the first to provide evidence to demonstrate the positive effect of ST on growth.

Recombinant DNA is a term which describes the splicing together or recombining of two or more pieces of DNA. The recombinant DNA techniques used to produce recombinant BST involves: the cloning of DNA (cDNA) from BST mRNA, the recombining of the BST cDNA with bacterial plasmid DNA and re-insertion of the "hybrid" DNA into *Escherichia Coli* bacteria for eventual expression of recombinant BST. The recombinant bacteria are grown in large numbers in typical fermentation vats, and the recombinant BST product extracted and purified. These same procedures are currently being used to produce human somatotropin and insulin for the treatment of dwarfism and diabetes mellitus, respectively.

Of the four recombinant BST products that have been produced by U.S. pharmaceutical companies and submitted for FDA approval for use in lactating cows, one is identical in amino acid sequence to endogenous BST, while the other three differ only slightly at the NH_2-terminus end of the protein. Recombinant BST is immunologically indistinguishable from endogenous BST using standard radioimmunoassay procedures.

The first experiment to be conducted with recombinant BST was a short-term study with lactating dairy cows which demonstrated that endogenous BST and recombinant BST were similar in increasing milk yields. The first experimental application of the use of recombinant ST to enhance growth was conducted with pigs.

COST-EFFECTIVENESS OF RECOMBINANT BST

Assuming recombinant BST were to be approved, the eventual adoption of recombinant BST by the beef industry and its cost effectiveness to the consumer will, among other things, be dependent upon: 1 - recombinant BST's ability to enhance growth performance and feed efficiency, *i* - the ability of recombinant BST to enhance lean tissue growth, 3 - consumer acceptance of leaner beef, 4-market value of leaner beef and 5-cost and delivery of recombinant BST.

The efficacy of recombinant BST for use as an anabolic agent in cattle to enhance the production of lean beef can not be fully accessed due to the limited amount of research that has been conducted with beef cattle to date.

An excellent 1989 review of the studies conducted through 1988 on the effects of BST on productivity in ruminants. Results of nine longer term trials (≥ 100 doses of BST treatment) concluded with cattle, indicate that BST treatment increased growth rates by approximately 12 percent with the range of responses being from 3 percent to 25 percent

EFFECT OF RECOMBINANT BST ON THE NUTRITIONAL VALUE OF BEEF PRODUCTS

Although the growth responses in cattle to recombinant BST have been variable, most studies have shown that BST is effective at increasing the lean:fat ratio in the carcass. In a recent study recombinant BST provided for 112 days increased daily protein gain by 16 percent and daily fat gain also tended to be lower (20 percent) in BST-treated steers. In other recent work, BST reduced the percent fat of the 9-10-11 rib section (indicator cut of carcass composition) by 13.4,21.2 and 54.4 percent with increasing dosage of BST. Recombinant BST in our studies has also been shown to be effective in growing beef heifers, where 9-10-11 rib sections from BST treated heifers contained more protein (16.3 vs 18.3 percent) and less fat (26.0 vs 16.5 percent). Earlier research indicated that carcass leanness was increased by both BST and estradiol and that the responses were additive suggesting that the mode of actions for these anabolic agents may be independent. Recent research also suggests that the anabolic response to BST is very much dependent upon dietary protein and energy levels.

EFFECT OF RECOMBINANT BST ON THE SAFETY OF BEEF PRODUCTS

Since 1985, pharmaceutical companies seeking approval for the use of recombinant BST in lactating dairy cows have had FDA authorization to market meat and milk from BST-treated cows. This decision was based on their evaluation of extensive toxicological data and review of scientific literature concerning BST. As a result of consumer concern and due to general misunderstanding of human food safety of BST, FDA in an unprecedented action, released results of experimental data that had been submitted to the FDA by the pharmaceutical companies seeking recombinant

BST approval. The results of these studies were recently published and provide an excellent review of pertinent scientific studies which were used as the basis for the decision to authorize zero day withdrawal for the consumption of milk and meat from recombinant BST-treated cows.

For years it has been known that pituitary BST is ineffective when administered to humans. Although pituitary derived human ST and BST both have 191 amino acids, there is approximately a 35 percent difference in their amino acid sequence. The amino acid sequence of recombinant BST products and pituitary BST are either identical or differ by only a few amino acids at the NH_2 terminus. Because BST is a protein, it will be degraded in the gastrointestinal tract just like any other protein. The product of protein digestion (amino acids) generally enter the blood circulation almost entirely as free amino acids. In order to obtain authorization for a zero day withdrawal for the marketing of milk and meat from cows treated with BST, each pharmaceutical company seeking recombinant FDA approval had to conduct studies demonstrating the oral inactivity of their individual recombinant BST products.

INSULIN-LIKE GROWTH FACTOR I (iGF-1)

Another concern that has been raised with regards to potential harmful effects due to ingestion of BST-treated milk or meat involves IGF-I. Indeed, IGF-I levels are regulated by ST and elevated levels of IGF-I have been found in plasma, milk and meat of bST treated cows, and there exists 100 percent homology between bovine IGF-I and human IGF-I (identical amino acid sequences). However, these concerns have no scientific basis. First IGF-I, like ST and all proteins, will be digested to amino acids. Secondly, IGF-I levels in human breast milk have been shown to be seven to eight ng per ml and 19 ng per ml at six to eight week postpartum. These levels of IGF-I are much higher than IGF-I levels that have been found in milk obtained from cows treated with recombinant BST. Although pasteurization of milk will not destroy IGF-I levels, the heating process that milk is subjected to in the preparation of infant formula denatures all but approximately one tenth of the IGF-I present.