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BRIEF COMMUNICATION

The process and technologies of gene discovery to application in dairy cattle

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The heady days of biotechnology that were driven by the assumption that biotechnology would solve all biological problems with simple solutions, are over. The 'biotech' investment in the mid to late 1990's was driven predominantly by commercial and scientific enthusiasm, ignoring biological, commercial and regulatory realities. In the post-bubble environment, the dairy industry, including ViaLactia Biosciences and our research partner Livestock Improvement Corporation are undertaking a research program endeavoring to align the expectations of the market, the investors and the limits of technology. In general, the thrust has been to utilize existing or develop new biological resources and where they are required and not available, tools for discovery. Much of

the on-going challenge is in defining the opportunity (desired phenotype), predicting technological developments, large scale investment in the public domain and matching the approach to the problem within time and budgetary constraints. Our approach will be presented with some examples of successes.

Background

The assumption made in the early to mid 1990's by investors was that biotechnology was sufficiently mature to enable the development of high value products principally, but not limited to, in the pharmaceutical area. Obviously, a considerable part of this investment was driven from the limited knowledge of the financial

markets which had little or no understanding of the technology or how it could be applied. Post-bubble, there is an understandable nervousness of investors, concerned about sunk investment or those contemplating even low level exposure. In the dairy industry the situation is no different with the industry, quite rightly, wanting a substantial return on its investment.

Consequently, the drive for investment efficiency particularly towards short term return, partly to allay concerns of whether the technology is appropriate or affordable for the industry, is strong. This expectation is overlaid on a rapidly moving field in which new technologies are constantly being introduced, or discarded, where the costs for some of the mature technologies is falling rapidly and, very significantly, the human and mouse genomes are completed and the bovine genome is not far away.

The dairy industry's product mix requirements also is undergoing a change from a commodity focus to incorporate differentiated dairy products derived from segregated milk supplies. In addition, in Europe, USA and other high intensity farming countries traits other than production including fertility, animal health and environmental impact of intensive farming are arguable more important than productivity. New Zealand produces around 2.5% of the world's milk and therefore there are significant markets for I.P. derived from a successful research program.

Three other significant developments help set the scene. The first is the realization that a biotechnology company needs a route to market as very little of the value can be captured directly from selling I.P. This understanding was surprisingly belated for some early in the biotech field and resulted in large sums being paid for 'seed' companies, with a subsequent devaluation of this investment when the value of this could not be realized, or eventual absorption into a larger entity. The second development is the requirement of proof of gene function for a robust patent position which devalued companies with patent portfolios based on EST filings at worst (raw un-annotated DNA sequence) or theoretically predicted gene function at best. The third development is the well published regulatory hurdles for the introduction of GM products.

ViaLactia BioSciences was established in the latter part of the 1990's with funding from the New Zealand Dairy Board, but with the clear understanding that it would become part of Fonterra. The founding expectation was to capitalize on the emerging technology particularly in genomics and functional genomics/systems biology. Although not decided at the time of ViaLactia's formation, there was an expectation (now realized) that VLB would work closely in partnership with the Livestock Improvement Corporation now under a joint venture called boviQuest. As part of Fonterra, boviQuest has access to the majority of New Zealand's farmers and an infrastructure that enables the seamless transition from production to consumer. LIC had seen the potential of Biotechnology and had commenced an investment in Partnership with CR Delta

(Holland Genetics) developing a research program with Professor Michel Georges at the University of Liege.

boviQuest's science platform is built largely on a 'phenotype-first' approach. The primary focus of boviQuest is to explore the natural variation in the bovine population and identify markers for use in marker assisted selection, and in some cases the gene responsible for the phenotype. With the associated phenotype providing proof of gene function, the discovery can be protected and therefore provide an economic advantage for the New Zealand Dairy industry. Implementation through selection or expansion of populations carrying rare variants is also relatively straightforward, avoiding the regulatory challenges and cost of a transgenic approach. This approach follows a well worn path in human and model system genetics. Indeed gene discovery, proof of function and variation of gene function in bovine are established through cross species comparisons.

Biological Resources

A phenotype first approach depends on access to well characterized animal populations. boviQuest has access through LIC and Fonterra to the majority of New Zealand's dairy herd giving an unprecedented opportunity to explore large half sib families and small groups of animals with extreme phenotypes. Research undertaken by the University of Liege and boviQuest has identified amino acid substitutions in two genes (DGAT 1, and GHR) responsible for two of the major production QTL's. Both loci were mapped through a conventional QTL approach leading to fine mapping and haplotype analysis. Ultimately the genes were discovered by mutation analysis in segregating sires of candidate genes. The effects were confirmed by the analysis of large populations. The use of these variations for selection has been patented and they are being applied in New Zealand by LIC. They are also being marketed internationally by boviQuest. (Grisart et al, Blott et al)

The limitation on further gene discovery in the national herd is clearly limited by the phenotypes that have been collected. To date, herd test/production data has been the focus of the work. The challenge will be to develop other relevant, inexpensive (per animal) phenotype measures.

In addition to the discovery of the two production related genes, boviQuest has also identified the gene responsible for epidermolysis bullosa (EB) in the offspring of a sire being tested in LIC's sire proving scheme. EB is a rare mechanobullous skin disorder that presented clinically as the loss of skin and mucosa from contact areas and resultant inflammation in some animals. Examination of skin samples from affected animals under light microscopy revealed separation of the epidermis from the underlying dermis. Electron microscopic analysis refined the site of cleavage to above the basement membrane and involving lysis of basal keratinocytes. These observations were consistent with the simplex form of epidermolysis bullosa (EB simplex) in humans. A mutation was identified in the KRT5 gene and displayed a dominant pattern.

Friesian Jersey Cross bred trial JXB

This is a very large investment of time and resources designed to take advantage of the genetic variation between breeds and within sire families. It consists of 850 F2 FJX cows divided into two cohorts. This trial will be described in more detail by Richard Spelman (LIC) at this meeting.

Microarray platform development

boviQuest identified microarrays as a key technology early in development. ViaLactia has developed an in-house array platform based on technologies sourced from Agilent Technologies using sequence generated from in house cDNA libraries. The Agilent arrays are fabricated through the synthesis of DNA oligonucleotides in situ on glass slides. This approach has the benefit that there is no large upfront consumable cost and that the array design can be changed quickly, important as more genome sequence become available. The arrays consist of 22,000 features designed to the 3' end of the sequence to avoid cross hybridization of gene families. Control experiments show that this platform delivers very reproducible results and will be a powerful method for phenotype definition and gene discovery.

CONCLUSION

With on-going method development and the soon-to-be available bovine genome there are very few technology limitations for marker and gene discovery. The major challenges are phenotype definition methods, access to well-characterized populations, and the relative cost for undertaking the research. In addition there will be significant challenges gaining farmer acceptance particularly if the application involves incurring significant cost and the introduction of multiple traits.

Along with adding value through commodity milk production biotechnology is expected to be a key driver in the development of specialty milk products. An indication of how the consumer market may evolve is evident in "wellness medicine" research. The primary aim is to predict propensities to common diseases such as heart disease or obesity through genetics and suggest lifestyle changes. This will result in a further fragmentation of the consumer market requiring food solutions. The application of biotechnology through genetics to differentiate food sources is a cost effective way to meet these requirements.

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