

Breeding Focus 2014 - Improving Resilience

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Contents

Preface	iii
Breeding disease resilient pigs <i>Susanne Hermes</i>	5
Inferring genetic resilience of animals to infectious pathogens - opportunities and pitfalls <i>Andrea B. Doeschl-Wilson and Graham Lough</i>	19
On-farm measures to monitor the health and immune status of pigs <i>Alison M. Collins</i>	31
Immune competence in livestock <i>Brad C. Hine, Bonnie A. Mallard, Aaron B. Ingham and Ian G. Colditz</i>	49
Performance and resilience of poultry in Thailand <i>Siriporn Tongsir and M. Gilbert Jeyaruban</i>	65
Breeding Sydney rock oysters and its effects on resilience <i>Wayne A. O'Connor, Michael C. Dove, Emma L. Thompson, Laura M. Parker, Pauline M. Ross and David A. Raftos</i>	73
Breeding barramundi for resilience in the face of global climate change <i>Dean R. Jerry, Carolyn S.K. Smith-Keune, Lauren Hodgson and Jeremy van der Waal</i>	87
Genetic variation of handling resilience of Tasmanian Atlantic salmon affected by amoebic gill disease (AGD) <i>Richard S. Taylor, Peter D. Kube, Brad S. Evans and Nick G. Elliott</i>	101
Resilience, tolerance, robustness and genotype x environment interaction in Merino sheep breeding <i>Sonja Dominik and Andrew A. Swan</i>	115
Robustness as a breeding objective for sheep in New Zealand <i>Mark J. Young and Beverley C. Thomson</i>	129
Breeding for resilience and resistance in Merino sheep <i>Sam F. Walkom and Daniel J. Brown</i>	141

Immune competence in livestock

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Abstract

Selection for production traits with little or no emphasis on health-related traits has led to an increase in the incidence of disease in many of our livestock species. Currently we are developing testing procedures to assess 'general immune competence' of beef cattle, dairy cattle and sheep on-farm. Immune competence traits will be combined with measures of temperament and ability to cope with management induced stress to estimate an animal's resilience. By exploring associations between resilience and important production traits we aim to develop breeding strategies which will identify animals highly suited to their production environment.

Introduction

The immune system is composed of tissues, cells and molecules which work together to protect the host animal against disease. Effective host defence is reliant on the immune system's ability to detect a wide variety of agents, to distinguish whether such agents are part of the body or foreign (self versus non-self), to determine whether non-self agents are commensals or threats, and to eliminate the potentially infectious agents or pathogens. Livestock, with the exception of those raised in specialised facilities, are exposed to a myriad of pathogens on a regular basis. Such pathogens possess the inherent ability to evolve rapidly, and as a consequence, adapt quickly to changes in the environment, and continually develop new strategies to avoid detection and elimination by the host's immune system. To detect and eliminate pathogens, the immune system has developed a diverse range of defensive responses that work together and which can be broadly categorised as either innate or adaptive responses. When a pathogen is first encountered, the innate immune system is activated. In the initial phases of the innate response, pre-formed anti-microbial substances, present in bodily fluids and secretions, begin to weaken and kill the pathogen while sending signals to alert the adaptive immune system of impending danger. As these responses advance, innate effector cells recognising common pathogen-associated signatures become activated, setting in motion a signalling cascade that

triggers defence mechanisms aimed at eliminating the pathogen. Should a pathogen breach these initial lines of defence and damage the host, mechanisms are in place to trigger adaptive immune responses. In contrast to innate responses which are largely non-specific, fast acting and not substantially enhanced by repeated exposure to the same pathogen, adaptive responses are highly pathogen-specific, slower to develop and continually refined upon repeated exposure to the same pathogen. Adaptive responses have an important memory component, which enables the effector functions of the adaptive immune system to be deployed more rapidly and with increasing specificity upon re-exposure to a pathogen.

The immune system is the body's main defence against disease, however some commonly used terms describing an individual's response to disease should be considered. Different disciplines and research studies use the related terms of disease resistance, tolerance, resilience and robustness in slightly different ways and therefore the precise relationship between these terms may be context specific. For the purpose of this paper the following distinctions will be made between these separate, yet related, terms as they pertain to disease. Disease resistance is considered as the host's ability to limit or eliminate pathogens using a variety of host defence reactions including physiological, behavioural and immunological responses (Colditz, 2008). Morphological traits can also make an important contribution to disease resistance as evidenced by the relationship between breech conformation and resistance to flystrike in Merino sheep (Greeff *et al.*, 2014). These various defence mechanisms work in conjunction to block pathogen invasion or destroy the invader. However, the host can also defend itself by limiting the damage caused by the pathogen using mechanisms that prevent self-harm or modulate escalating immune responses (Schneider and Ayres, 2008). This is termed disease tolerance, or in other words, an ability to minimise the effects of infection at a given level. This terminology can be further refined by identifying individuals that maintain productivity in the face of a disease challenge. This is generally referred to as disease resilience (Bishop and Morris, 2007). A key difference between disease tolerance and disease resilience is that disease tolerance often implies a permanent state of infection where repeated exposure to a particular pathogen reduces sensitivity to its effects, whereas disease resilience is generally considered a more transient state of infection where the host eventually clears the infection with little or no effect on production. Finally, the term robustness is defined as the ability of the individual to maintain its functions in the face of internal and external challenges (Kitano, 2007). Robustness therefore is quantified by performance of various traits, such as growth, fertility, and carcass characteristics, as well as response to disease.

Both the ability to resist infection and the ability to tolerate the effects of disease are likely contributors to an animal's ability to maintain productivity when faced with a disease challenge. Therefore disease resistance and disease tolerance can both be considered to contribute to disease resilience (Bishop, 2012). In considering whether to target, disease resistance or disease tolerance, as the basis for improving animal health in selective breeding programs, there are no simple answers. It is important however to realize that disease resistance and disease tolerance are generally negatively correlated, and are based on different underlying host mechanisms and genes, and have different impacts on the evolving pathogen (Simms and Triplett, 1994). Because disease resistance and disease tolerance are often negatively genetically correlated,

individuals identified as susceptible to disease tend to be more tolerant. Conversely, individuals with resistant genotypes tend to be less tolerant. The implication of these factors is outside the scope of this discussion; however, it highlights the importance of considering the preferred final outcomes for both the host and pathogen when establishing selection strategies to improve animal health. The research described here focuses on general disease resistance because in many cases of infectious disease it is critical to eliminate the causal agent in order to prevent mortality and unintended pathogen transmission to the environment or to other hosts. Furthermore, animals identified using appropriate strategies as having enhanced general disease resistance are likely to be resistant to a wide-range of pathological agents.

When developing strategies aimed at improving animal health, it is important to recognise that disease resilience is just one component of general resilience. Just as disease resilience can be considered as the ability of an animal to maintain productivity in the face of disease challenge, general resilience can be considered as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Livestock are exposed to a variety of environmental challenges in their production environment including abiotic extremes, social and management-induced stressors and disease challenges. The contribution of immune competence to general resilience will be discussed in further detail later in the chapter.

Immune competence

Immune competence can be considered as ‘the ability of the body to produce an appropriate and effective immune response when exposed to a variety of pathogens’ (Wilkie and Mallard, 1999). Weak responses may allow pathogens to persist or overcome host defences leading to morbidity and mortality. Inappropriate responses to self antigens (an antigen being any substance that provokes an adaptive immune response can lead to autoimmune diseases, while inappropriate responses to harmless antigens can lead to allergic responses. It is also critical that when faced with a pathogen challenge, the body mounts the most effective type of response to control that pathogen. Some pathogens have devised means by which they enter cells of the body (intracellular pathogens) while others remain in the environment external to cells (extracellular pathogens). Elimination of intracellular pathogens generally requires that infected cells be destroyed. This job is carried out by phagocytes, which are specialised cells with the ability to ingest harmful agents and infected cells, and by cytotoxic cells, which are capable of inducing programmed cell death in target cells. Collectively, the actions of such cells are described as ‘cell-mediated immune responses’. In contrast, extracellular pathogens and soluble antigens are more effectively controlled by ‘antibody-mediated immune responses’. Antibodies bind to pathogens and soluble antigens in the extracellular environment, preventing them from damaging or entering cells and tagging them for destruction by immune cells. As the immune system is constantly challenged by both intracellular and extracellular pathogens it is critical that individuals have a balanced ability to mount both cell-mediated and antibody-mediated immune responses. Equally responses must be of a magnitude that effectively eliminates pathogens without causing self harm.

Immune competence - an important selection trait

Selection for production traits with little or no emphasis on health and fitness traits has led to an increase in the incidence of disease in many livestock industries. Antagonistic or unfavourable genetic correlations exist between production traits and the incidence of many common diseases in livestock (Rauw *et al.*, 1998). For example, the genetic correlation between milk production and the incidence of mastitis in dairy cattle has been estimated at between 0.15 to 0.37 (Lyons *et al.*, 1991; Uribe *et al.*, 1995; Van Dorp *et al.*, 1998). Thus progeny of parents with high genetic potential for milk production have a higher incidence of mastitis than progeny of parents with low genetic potential for milk production. In pigs, selection focussed on high productivity has led to an increase in susceptibility to stress and disease (Prunier *et al.*, 2010). In sheep, recent production focussed breeding has been achieved in an environment where chemicals have been available to control the major pathogens, gastrointestinal nematodes. A comparison of progeny sired by contemporary rams or from semen collected over 30 years ago shows advances in many productivity traits during this time however natural resistance to nematodes has declined significantly (Shaw *et al.*, 2012). Such findings suggest that continued selection based on productivity alone will result in further increases in the incidence of disease in livestock species. The animal production sector is becoming increasingly aware of this issue and is actively seeking solutions to the problem.

Changes in community attitudes are also contributing to a renewed focus on breeding production animals that have an enhanced natural ability to resist disease. Consumer awareness of practices that impact the health and welfare of food-producing animals is increasing, as is concern regarding the use of antibiotics to control disease in livestock and the potential food contamination issues that arise from their misuse. However, it must also be acknowledged that selection for increased productivity remains a key profit driver for our livestock industries. Alternative strategies that address these consumer concerns while reducing the incidence of disease, and as a consequence, production losses and treatment costs associated with disease are therefore required. It is therefore proposed that a possible genetic solution is to combine production traits and immune competence traits into a weighted selection index with the aim of breeding high-producing animals with enhanced general immune competence (Mallard *et al.*, 1998a; Wilkie and Mallard, 1999).

Selecting for resistance to specific diseases versus selection for general disease resistance

Breeding strategies targeted at increasing resistance to specific diseases in livestock have proven very successful. Such strategies include breeding sheep with enhanced resistance to specific internal parasites (Le Jambre *et al.*, 1971), dairy cattle with enhanced resistance to mastitis (Heringstad *et al.*, 2000) and beef cattle with increased resistance to brucellosis (Adams and Templeton, 1993) and to cattle ticks (Frisch and O'Neill, 1998). Based on the knowledge that the host immune system tailors responses to the type of pathogen encountered, it could be expected that selection of animals based on their resistance to a specific disease may inadvertently

increase their susceptibility to other diseases. For example, selection of animals based on their resistance to an extracellular pathogen, largely controlled by an antibody-mediated immune response, might inadvertently increase their susceptibility to intracellular pathogens, largely controlled by cell-mediated immune responses. In support of this concept, it has been reported that cell-mediated and antibody mediated immune responses are negatively genetically correlated in dairy cattle even though they work in coordination to protect the host (Hernandez *et al.*, 2006; Thompson-Crispi *et al.*, 2012b). An inverse relationship between antibody production and macrophage function, an important component of cell-mediated immunity, was first reported in Biozzi mice selected for high and low antibody production (Hale and Howard, 1981). A similar relationship has since been reported in cattle selected for resistance or susceptibility to *Brucella abortus* (Price *et al.*, 1990). Furthermore, a recent study in dairy cattle has demonstrated that cattle which test positive for tuberculosis, which is largely controlled by cell-mediated immunity, have a lower incidence of mastitis, largely controlled by antibody-mediated immunity (Edwards, 2014). In contrast to these findings, monocyte function was found to be similar in pigs selected for high and low overall immune responsiveness (Groves *et al.*, 1993). Although such findings suggest more research is required to assess the long term effects of selection for resistance to a specific disease on susceptibility to other diseases in livestock, long term benefits can be expected from adopting breeding strategies based on enhancing general disease resistance of livestock as an alternative to, or in conjunction with, enhancing resistance to specific diseases of significant economic importance to the livestock industries.

Assessing immune competence

Genetic variation in the ability to resist disease is due to a large number of additive genetic effects which together regulate innate and adaptive immune responses (Wilkie and Mallard, 1999). It has been estimated that greater than 7% of all known genes in the mammalian genome are involved in immune function (Kelley *et al.*, 2005). Although the underlying genotype involves complex interactions between many genes, by inducing immune responses and objectively measuring such responses in livestock, general immune responsiveness of individual animals can be assessed (Wilkie and Mallard, 1999) (Fig 1.). This was first demonstrated amongst livestock species in Yorkshire pigs, where measures of innate and adaptive immunity (both antibody and cell-mediated) were combined to generate estimated breeding values (EBVs) for general immune responsiveness and to rank boars and gilts as high, intermediate and low immune responder (IR) phenotypes for use in future breeding programs (Mallard *et al.*, 1992). This strategy aimed to simultaneously improve the ability of animals to mount both antibody and cell-mediated responses, and as a consequence, enhance general disease resistance. Following the inbreeding of high, intermediate and low IR phenotype pigs for several generations it was found that high IR pigs had superior antibody responses to test antigens and several commercial vaccines (Wilkie and Mallard, 1999), a lower frequency of non-responders when vaccinated with inactivated influenza vaccine (Wilkie and Mallard, 1998) and higher antibody avidity, a measure of the strength of the antibody-antigen interaction (Appleyard *et al.*, 1992), than their intermediate and low IR counterparts. Although such findings provide overwhelming evidence to suggest that selection successfully enhanced general immune responsiveness in

high IR pigs, when challenged with *Mycoplasma hyorhinis*, these pigs displayed more severe arthritis than LR pigs, suggesting that high IR phenotype pigs may be more prone to generating inflammatory responses (Magnusson *et al.*, 1998). However, in the same study, high IR pigs were found to have less severe peritonitis, less severe pleuritis and produced serum antibody against *M. hyorhinis* both earlier and to a higher level than did their low IR counterparts and therefore survived better. Thus the tradeoff between lameness and survival may be defensible in this case.

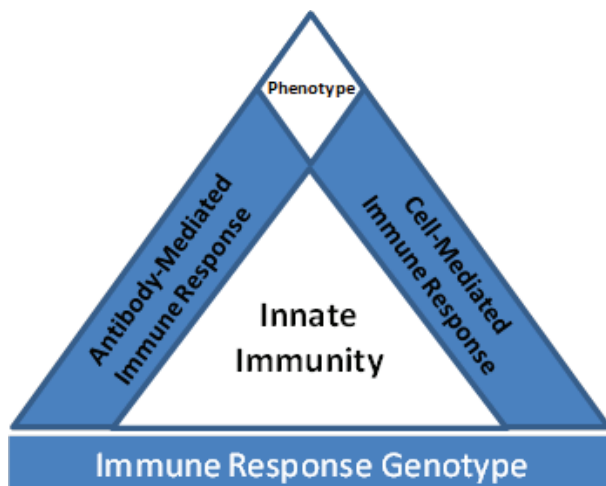


Figure 1. Genetic variation in the ability to resist disease is due to a large number of additive genetic effects which together regulate innate and adaptive immune responses (Source: adapted from Wilkie and Mallard, 1999)

More recently, research efforts have been focussed on developing protocols to assess general immune responsiveness in dairy cattle, similar to those used in pigs, and on investigating associations between immune responsiveness phenotypes and the incidence of disease in large-scale commercial dairy farms. This strategy involves immunising animals with antigens that stimulate either strong antibody or cell-mediated immune responses, and then measuring both types of response. The responses are then used in combination to rank animals for general immune responsiveness (Heriazon *et al.*, 2009a; Heriazon *et al.*, 2009b). Although this ranking strategy does not incorporate measures of innate immunity, in contrast to the strategy used in pigs, it is acknowledged that strong adaptive immune responses are underpinned by strong innate immune responses (Fig 1.). In fact, macrophage function, including both phagocytosis and nitrous oxide production, seems to be stronger in high responder dairy cows (BA Mallard, *pers. comm.*) as does TLR2 expression, a receptor involved in the recognition of a wide array of microbial molecules (Wagter-Lesperance *et al.*, 2014). Therefore such a strategy can still be expected to identify animals with enhanced general immune responsiveness and, as a consequence, general disease resistance. Researchers have utilised this testing strategy to investigate

the influence of hybrid vigour on general immune responsiveness in purebred and crossbreed dairy cattle (Begley *et al.*, 2009, Cartwright *et al.*, 2012), the influence of age and pregnancy status on general immune responsiveness in dairy heifers (Hine *et al.*, 2011), leukocyte (white blood cell) populations in high and low IR dairy heifers (Hine *et al.*, 2012) and the influence of geographical location on immune response profiles of Canadian dairy cattle (Thompson-Crispi and Mallard, 2012).

Heritability of immune competence traits

The practicality and efficiency of the immune response testing protocol, developed by Mallard and colleagues for use in dairy cattle, has permitted the testing of large numbers of commercial dairy cows across diverse geographical locations in North America in order to estimate the heritability of immune responsiveness traits (Thompson-Crispi *et al.*, 2012b). The heritability of a trait refers to the proportion of the observed variation between animals which can be directly attributed to differences in genetics. Genetic gains can be made quickly in highly heritable traits, whereas genetic progress in traits with low heritability, while still achievable, is expected to be proportionally slower. The heritability of antibody and cell mediated immune responsiveness in commercial dairy cattle has been estimated at 0.16-0.41 (with a standard error (SE) of 0.09-0.11, depending on time of sampling and antibody isotype measured) and 0.19 (SE = 0.10), respectively (Thompson-Crispi *et al.*, 2012b). These estimates are in line with those reported in pigs selected for general immune responsiveness for eight generations, where the heritability of antibody and cell-mediated immune responsiveness was estimated at 0.27 and 0.16, respectively (Wilkie and Mallard, 1999). Heritability estimates of these traits in the initial cohort of Canadian Holstein sires owned by the Semex Alliance (<http://www.semexusa.com/>) are in the range of 0.3 to 0.48 (BA Mallard, *pers. comm.*). These heritability estimates are considered moderate and they are comparable with the heritability of many highly selected production traits in livestock species (Safari and Fogarty, 2003). Therefore, reasonable genetic gains in general immune responsiveness traits can be expected when the traits are incorporated into livestock breeding programs.

Selection for immune competence - associations with disease incidence, reproduction and productivity

Knowledge of associations between enhanced general immune responsiveness and incidence of disease, rates of reproduction and productivity in commercial livestock operations is critical to the success of selection strategies aimed at breeding high-producing animals with enhanced general immune responsiveness. In an early study conducted on both research and commercial dairy farms, it was reported that cows classified as high for antibody-mediated immune responsiveness had a lower incidence of mastitis when compared with average or low responders using data pooled across herds. High antibody responder cows also responded better to the commercial *Escherichia coli* J5 mastitis preventative vaccine (Wagter *et al.*, 2000). It should be noted however, that in the same study, cows classified as high antibody responders had the

highest incidence of mastitis in one of the three herds tested, with all mastitis cases in these cows recorded in first-parity cows rather than multiparous cows. This finding was limited to the research herd tested and was not observed in the two commercial herds tested. Disease incidence records carefully and systematically collected on commercial farms provide valuable data to quantify the success of selecting for improved general disease resistance (Guy *et al.*, 2012). A more recent study reported incidence rates of clinical mastitis in 41 herds across Canada in dairy cattle classified as high, average or low for general immune responsiveness (Thompson-Crispi *et al.*, 2013). Results from this study revealed that the average cases of mastitis reported per 100 cow years in high, average and low IR cows were 17.1, 27.9 and 30.7, respectively and that severity of mastitis cases was greatest in low IR cows. Associations between disease incidence and general immune responsiveness have also been investigated in a large commercial dairy herd in Florida (Thompson-Crispi *et al.*, 2012a). Results showed that the incidence of mastitis was higher in average IR cows compared to high IR cows. Mastitis incidence tended to be higher in low IR as compared to high IR cows; however, the difference was not statistically significant. Although observed differences in the incidence of metritis and ketosis between IR phenotypes were not significant, displaced abomasums and retained foetal membranes were observed more frequently in low IR cows. The considerable research effort aimed at developing a strategy to assess general immune responsiveness and evaluating the success of that strategy to reduce the incidence of disease in commercial dairy herds has culminated in the licensing of the High Immune Response technology to the Semex Alliance. The Semex Alliance has been marketing semen from dairy sires with EBVs for enhanced general immune responsiveness in North America since January 2013 and is currently marketing this semen globally. Recent data collected from large commercial dairy farms in the United States demonstrated that daughters of Immunity+ sires have lower incidence of mastitis (8.8% versus 15.8%) and pneumonia (6.8% versus 9.1%) than do daughters from non-Immunity+ bulls in the same herd (Data courtesy of Jay Shannon, Sire Analyst, Semex Alliance).

It has long been considered that resistance to disease in livestock may incur a production cost as a consequence of nutrients being redirected from production to support immune function. However counter-balancing this cost of resistance is the metabolic cost of disease (reviewed by Colditz, 2002; Colditz, 2008). Chronic activation of immune defence pathways during chronic subclinical infection leads to reduced efficiency of production. Enhanced immune responsiveness is expected to avoid the penalty to production that accompanies chronic immune activation and therefore may lead to improved productivity. In support of this concept, high IR pigs were found to have higher growth rates relative to their intermediate IR and low IR counterparts, significantly reducing the time taken to reach market weight (Mallard *et al.*, 1998a). The relationship between antibody-mediated immune responsiveness and milk production has also been investigated in dairy cows. Among multiparous cows, high IR animals were found to have significantly higher milk production compared with low IR animals; however, in first-parity cows, milk production was higher in low IR animals than in average of high IR cows (Wagter *et al.*, 2003). Favourable associations between general immune responsiveness and reproductive traits in dairy cattle have also been reported (Thompson-Crispi *et al.*, 2012b). In a study across 42 herds in Canada, favourable associations were observed between general immune responsiveness and number of artificial services, and time from first service to conception.

Clearly more research is required to determine associations between general immune responsiveness and important reproduction and production traits in livestock species. It is important to recognise however, that regardless of the outcome of these studies, genetic progress can be made simultaneously in traits even when those traits are unfavourably correlated. An example of this comes from the sheep industry where genetic progress in reducing fibre diameter while simultaneously increasing fleece weight, traits which are unfavourably correlated, has been successful (Taylor and Atkins, 1997).

Phenotype to genotype

General immune responsiveness is a complex trait under polygenic control, having many genes each contributing to the variation observed in the trait (Wilkie and Mallard, 1999). Therefore it will be difficult to identify individual genes which have a major effect on general immune responsiveness which can be selected for in commercial populations of livestock. The use of EBVs or genomic based estimated breeding values (GEBVs) may help to overcome this issue by simultaneously selecting for genes contributing to the general immune responsiveness trait without the need to identify individual contributing genes (Thompson-Crispi *et al.*, 2014). Estimation of GEBVs for traits is based on genetic markers across the genome that have a statistical association with those traits. Genome-wide association studies (GWAS) can be undertaken to explore associations between genetic markers and traits of interest. Various GWAS have been conducted in livestock to evaluate genetic differences in production, reproduction and health traits (Cole *et al.*, 2011; Do *et al.*, 2014). Recently, a GWAS was conducted to evaluate general immune responsiveness in Canadian Holstein cattle (Thompson-Crispi *et al.*, 2014). This study identified several significant genetic markers, candidate genes and pathways associated with antibody and cell-mediated immune responsiveness in dairy cattle. Based on these findings it may be possible to calculate GEBVs for general immune responsiveness traits which could be incorporated into selection indices. However, studies based on larger reference populations are required to validate this approach. Associations between genetic markers and traits can differ between breeds and even between lines within breeds and therefore validation across multiple populations will be required.

Immune competence as a component of resilience

Resilience can be described as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Livestock respond to challenges from infectious agents and other environmental stressors through immunological, physiological and behavioural defence reactions. These three modalities of host defence are highly integrated and their activation uses resources that would otherwise be directed towards production (Colditz *et al.*, 2002). Research over a number of years has highlighted that the level of activity of the immune system is associated with an animal's ability to thrive in the face of environmental stressors and can be an indicator of future health and performance (Schmid-Hempel, 2003). Such findings highlight the important contribution of immune competence to resilience.

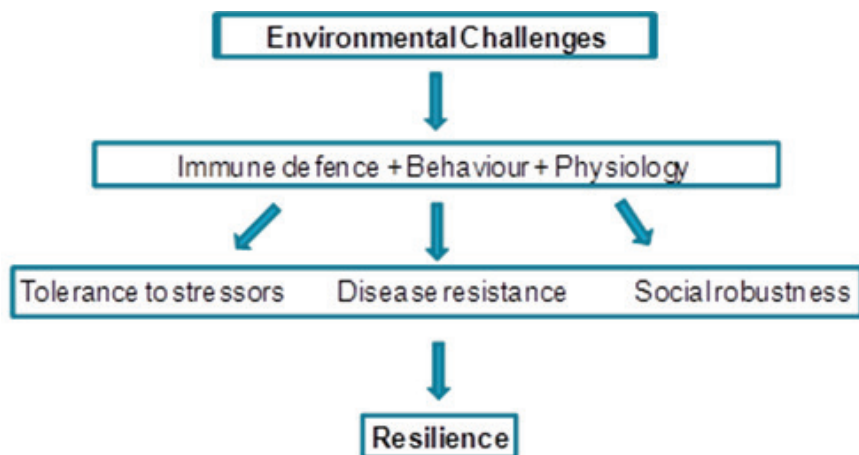


Figure 2. Resilience can be considered as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Measures of disease resistance, tolerance to stressors and social robustness can be used in combination to predict an animal's resilience

The resilience of individual animals can be predicted by combining measures of their general immune competence, stress responsiveness and behaviour or temperament (Fig. 2). Livestock management practices, such as weaning, social mixing and animal handling, provide opportunities to simultaneously assess the various components of host defence contributing to resilience. For example, yard weaning of beef calves provides an opportunity in which to simultaneously assess the ability of calves to cope with the stress induced by the weaning process, the ability of calves to respond to immunological challenges whilst under stress and also assess the temperament of calves. It is well recognised that stress, both physiological and metabolic, negatively impacts on immune function. For example, the incidence of disease in dairy cows is highest during the periparturient period when cows are under physical and metabolic stress (Mallard *et al.*, 1998b). Incidence rates of bovine respiratory disease in feedlot cattle are highest in the first few weeks after entering the feedlot when cattle are under stress as a consequence of adjusting to a new environment (Schnieder *et al.*, 2009) and the stress of late pregnancy and early lactation induces a relaxation in immunity to gastrointestinal parasites in sheep during the periparturient period is well documented (Salisbury and Arundel, 1970). Such findings suggest that assessing immune competence in animals when under stress may improve our ability to identify animals able to resist disease challenges during subsequent periods of heightened exposure to environmental stressors. When combined with measures of stress responsiveness and temperament, general immune responsiveness when under stress is expected to be a good predictor of resilience in livestock. Development of protocols to assess resilience phenotypes in livestock species will allow selection of animals better adapted to the environmental challenges associated with their respective production environments.

Summary

Selection for production traits with little or no emphasis on health and fitness traits has led to an increase in the incidence of disease in many livestock industries. A possible genetic solution to this problem is to develop breeding strategies aimed at enhancing general disease resistance of the animal while simultaneously making genetic gains in important production traits. Although immune responsiveness is a complex trait under polygenic control, general immune responsiveness can be assessed by inducing immune responses and objectively measuring such responses in livestock, allowing EBVs, and likely in the future, GEBVs to be calculated for individual animals. Selection for resistance to specific diseases carries the potential risk of inadvertently increasing susceptibility to other diseases. Selection of livestock for general immune responsiveness as an alternative to, or in conjunction with, selection for resistance to specific diseases reduces this risk and is expected to improve broad-based disease resistance. Extensive research in dairy cattle has demonstrated that animals with enhanced general immune responsiveness have a reduced incidence of disease in commercial herds. Furthermore, favourable associations between general immune responsiveness, production and reproduction traits have also been reported.

The ability to resist disease forms an important component of resilience, described as the ability to maintain productivity in the face of diverse environmental challenges. The resilience of livestock is becoming increasingly important as 1) selection pressure to increase productivity from livestock continues, 2) consumer awareness regarding the health and welfare of the animals producing their food increases and 3) consumer concern regarding the use of antibiotics in food-producing animals intensifies. The resilience of individual animals can be predicted using a combination of measures of general immune competence, stress responsiveness and temperament. Development of protocols to assess resilience phenotypes in livestock species will allow selection of animals better adapted to their production environment and help ensure the long-term future of livestock industries.

References

- Adams LG, Templeton JW (1993) Selection experiments to alter disease resistance traits in domestic animals. *Veterinary Immunology and Immunopathology* **38**, 387-394.
- Appleyard G, Wilkie BN, Kennedy BW, Mallard BA (1992) Antibody avidity in Yorkshire pigs of high and low immune response groups. *Veterinary Immunology and Immunopathology* **31**, 229-240.
- Begley N, Buckley F, Pierce KM, Fahey AG, Mallard BA (2009) Differences in udder health and immune response traits of Holstein-Friesians, Norwegian Reds, and their crosses in second lactation. *Journal of Dairy Science* **92**, 749-757.

Bishop SC, Morris CA (2007) Genetics of disease resistance in sheep and goats. *Small Ruminant Research* **70**, 48-59.

Bishop SC (2012) A consideration of resistance and tolerance for ruminant nematode infections. *Frontiers in Genetics* **3**, article 168.

Cartwright SL, Schaeffer LR, Burnside EB, Mallard BA (2012) Adaptive immune response, survival, and somatic cell score between postpartum Holstein and Norwegian red x Holstein first-calf heifers. *Journal of Animal Science* **90**, 2970-2978.

Colditz IG (2002) Effects of the immune system on metabolism: implications for production and disease resistance in livestock. *Livestock Production Science* **75**, 257-268.

Colditz IG (2008) Six costs of immunity to gastrointestinal nematode infections. *Parasite Immunology* **30**, 63-70.

Cole JB, Wiggans GR, Ma L, Sonstegard TS, Lawlor TJ Jr, Crooker BA, Van Tassell CP, Yang J, Wang S, Matukumalli LK, Da Y (2011) Genome-wide association analysis of thirty one production, health, reproduction and body conformation traits in contemporary U.S. Holstein cows. *BMC Genomics* **12**, article 408.

Do DN, Ostersen T, Strathe AB, Mark T, Jensen J, Kadarmideen HN (2014) Genome-wide association and systems genetic analyses of residual feed intake, daily feed consumption, backfat and weight gain in pigs. *BMC Genetics* **15**, article 27.

Edwards E (2014) 'Preliminary investigation into mastitis rates as a predictor for bovine tuberculosis susceptibility and the possibility of implementation of High Immune Response dairy cows.' BSc (Hons) thesis, Royal Agricultural University, Cirencester, UK.

Frisch JE and O'Neill CJ (1998) Comparative evaluation of beef cattle breeds of African, European and Indian origins. 2. Resistance to cattle ticks and gastrointestinal nematodes. *Animal Science* **67**, 39-48.

Greeff JC, Karlsson LJE, Schlink AC (2014) Identifying indicator traits for breech strike in Merino sheep in a Mediterranean environment. *Animal Production Science* **54**, 125-140.

Groves TC, Wilkie BN, Kennedy BW, Mallard BA (1993) Effect of selection of swine for high and low immune responsiveness on monocyte superoxide anion production and class II MHC antigen expression. *Veterinary Immunology and Immunopathology* **36**, 347-358.

Guy SZY, Thomson PC, Hermes S (2012) Selection of pigs for improved coping with health and environmental challenges: breeding for resistance or tolerance? *Frontiers in Genetics* **3**, 281:1-9.

- Hale C, Howard JG (1981) Immunological regulation of experimental cutaneous leishmaniasis. 2. Studies with Biozzi high and low responder lines of mice. *Parasite Immunology* **3**, 45-55.
- Heriazon A, Thompson KA, Wilkie BN, Mathes-Sears W, Quinton M, Mallard BA (2009a) Antibody to ovalbumin and delayed-type hypersensitivity to *Candida albicans* and mycobacteria in lactating Holstein cows using Quil A or Freund's complete adjuvant. *Veterinary Immunology and Immunopathology* **127**, 220-227.
- Heriazon A, Yager JA, Sears W, Mallard BA (2009b) Induction of delayed-type hypersensitivity and interferon-gamma to *Candida albicans* and anti-hen-egg white lysozyme antibody as phenotypic markers of enhanced bovine immune response. *Veterinary Immunology and Immunopathology* **129**, 93-100.
- Heringstad B, Klemetsdal G, Ruane J (2000) Selection for mastitis resistance in dairy cattle: a review with focus on the situation in the Nordic countries. *Livestock Production Science* **64**, 95-106.
- Hernández A, Quinton M, Miglior F, Mallard BA (2006) Genetic parameters of dairy cattle immune response traits. 8th World Congress on Genetics Applied to Livestock Production, 15-18.
- Hine BC, Cartwright SL, Mallard BA (2011) Effect of age and pregnancy status on adaptive immune responses of Canadian Holstein replacement heifers. *Journal of Dairy Science* **94**, 981-991.
- Hine BC, Cartwright SL, Mallard BA (2012) Analysis of leukocyte populations in Canadian Holsteins classified as high or low immune responders for antibody- or cell-mediated immune response. *Canadian Journal of Veterinary Research* **76**, 149-156.
- Kelley J, de Bono B, Trowsdale J (2005) IRIS: A database surveying known human immune system genes. *Genomics* **85**, 503-511.
- Kitano H (2007) Towards a theory of biological robustness. *Molecular Systems Biology* **3**, Article 137.
- LeJambre LF, Ractliffe LH, Uhazy LS, Whitlock JH (1971) Fecal egg output of lambs in relationship to *Haemonchus contortus* burden. *International Journal of Parasitology* **1**, 157-160.
- Lyons DT, Freeman AE, Kuck AL (1991) Genetics of health traits in Holstein cattle. *Journal of Dairy Science* **74**, 1092-1100.

Magnusson U, Wilkie B, Mallard B, Rosendal S, Kennedy B (1998) Mycoplasma hyorhinis infection of pigs selectively bred for high and low immune response. *Veterinary Immunology and Immunopathology* **61**, 83-96.

Mallard BA, Wilkie BN, Kennedy BW, Quinton M (1992) Use of estimated breeding values in a selection index to breed Yorkshire pigs for high and low immune and innate resistance factors. *Animal Biotechnology* **3**, 257-280.

Mallard BA, Wilkie BN, Kennedy BW, Gibson J, Quinton M (1998a) Immune responsiveness in swine: eight generations of selection for high and low immune response in Yorkshire pigs. 6th World Congress on Genetics Applied to Livestock Production, 1-8.

Mallard BA, Dekkers JC, Ireland MJ, Leslie KE, Sharif S, Vankampen CL, Wagter L, Wilkie BN (1998b) Alteration in immune responsiveness during the peripartum period and its ramification on dairy cow and calf health. *Journal of Dairy Science* **81**, 585-595.

Price RE, Templeton JW, Smith R 3rd, Adams LG (1990) Ability of mononuclear phagocytes from cattle naturally resistant or susceptible to brucellosis to control in vitro intracellular survival of *Brucella abortus*. *Infection and Immunity* **58**, 879-886.

Prunier A, Heinonen M, Quesnel H (2010) High physiological demands in intensively raised pigs: impact on health and welfare. *Animal* **4**, 886-898.

Hale C, Howard JG (1981) Immunological regulation of experimental cutaneous leishmaniasis. 2. Studies with Biozzi high and low responder lines of mice. *Parasite Immunology* **3**, 45-55.

Rauw WM, Kanis E, Noordhuizen-Stassen EN, Grommers FJ (1998) Undesirable side effects of selection for high production efficiency in farm animals: a review. *Livestock Production Science* **56**, 15-33.

Safari A, Fogarty NM (2003) Genetic parameters for sheep production traits. NSW Agriculture, Technical Bulletin 49 (NSW DPI: Orange, Australia).

Salisbury JR, Arundel JH (1970) Peri-parturient deposition of nematode eggs by ewes and residual pasture contamination as sources of infection for lambs. *Australian Veterinary Journal* **46**, 523-529.

Schmid-Hempel P (2003) Variation in immune defence as a question of evolutionary ecology. *Proceedings of the Royal Society of London* **270**, 357-366.

Schnieder DS, Ayres JS (2008) Two ways to survive infection: what resistance and tolerance can teach us about treating infectious disease. *Nature Reviews Immunology* **8**, 889-895.

Schneider MJ, Tait RG Jr, Busby WD, Reecy JM (2009) An evaluation of bovine respiratory disease complex in feedlot cattle: Impact on performance and carcass traits using treatment records and lung lesion scores. *Journal of Animal Science* **87**, 1821-1827.

Shaw RJ, Morris CA, Wheeler M, Tate M, Sutherland IA (2012) Salivary IgA: a suitable measure of immunity to gastrointestinal nematodes in sheep. *Veterinary Parasitology* **186**, 109-117.

Simms EL, Triplett J (1994) Costs and benefits of plant responses to disease: resistance and tolerance. *Evolution* **48**, 1973-1985.

Taylor PJ, Atkins KD (1997) Genetically improving fleece weight and fibre diameter of the Australian Merino – The Trangie QPLU\$ project. *Wool Technology & Sheep Breeding* **45**, 92-107.

Thompson-Crispi KA, Hine B, Quinton M, Miglior F, Mallard BA (2012a) Short communication: Association of disease incidence and adaptive immune response in Holstein dairy cows. *Journal of Dairy Science* **95**, 3888-3893.

Thompson-Crispi KA, Mallard BA (2012) Type 1 and type 2 immune response profiles of commercial dairy cows in 4 regions across Canada. *Canadian Journal of Veterinary Research* **76**, 120-128.

Thompson-Crispi KA, Sewalem A, Miglior F, Mallard BA (2012b) Genetic parameters of adaptive immune response traits in Canadian Holsteins. *Journal of Dairy Science* **95**, 401-409.

Thompson-Crispi KA, Miglior F, Mallard BA (2013) Incidence rates of clinical mastitis among Canadian Holsteins classified as high, average, or low immune responders. *Clinical and Vaccine Immunology* **20**, 106-112.

Thompson-Crispi KA, Sargolzaei M, Ventura R, Abo-Ismael M, Miglior F, Schenkel F, Mallard BA (2014) A genome-wide association study of immune response traits in Canadian Holstein cattle. *BMC Genomics* **15**, Article 559.

Uribe HA, Kennedy BW, Martin SW, Kelton DF (1995) Genetic parameters for common health disorders of Holstein cows. *Journal of Dairy Science* **78**, 421-430.

Van Dorp TE, Dekkers JC, Martin SW, Noordhuizen JP (1998) Genetic parameters of health disorders, and relationships with 305-day milk yield and conformation traits of registered Holstein cows. *Journal of Dairy Science* **81**, 2264-2270.

Wagter LC, Mallard BA, Wilkie BN, Leslie KE, Boettcher PJ, Dekkers JC (2000) A quantitative approach to classifying Holstein cows based on antibody responsiveness and its relationship to peripartum mastitis occurrence. *Journal of Dairy Science* **83**,488-498.

Wagter LC, Mallard BA, Wilkie BN, Leslie KE, Boettcher PJ, Dekkers JC (2003) The relationship between milk production and antibody response to ovalbumin during the peripartum period. *Journal of Dairy Science* **86**, 169-173.

Wagter-Lesperance LC, Hodgins DC, Emam M, Paibomesai MA, Mallard B (2014) Expression of TLR2 Pattern Recognition Receptor on Mononuclear Cells of Dairy Cattle Ranked using Estimated Breeding Values (EBV) of Adaptive Immune Response Traits. 10th World Congress on Genetics Applied to Livestock Production, article 548.

Wilkie BN, Mallard BA (1998) Multi-trait selection for immune response; A possible alternative strategy for enhanced livestock health and productivity. In 'Progress in Pig Science', ed J Wiseman, pp 29-38. (Nottingham University Press, Nottingham).

Wilkie BN, Mallard BA (1999) Selection for high immune response: an alternative approach to animal health maintenance? *Veterinary Immunology and Immunopathology* **72**, 231-235.