# Abstracts of Invited Lectures

# Interactions of metabolic challenges and productivity

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The onset of lactation in modern dairy cows is characterized by a negative energy balance, due to a drastic increase in energy requirements for milk yield and a simultaneous depression in dry matter intake around parturition. Prioritization of milk yield over maternal body functions is a universal biological strategy in all lactating mammals to buffer the newborn's nutrition from fluctuations in the dam's energetic status. Consequently, in case of an energy deficiency, the dam will mobilize fat and protein reserves in order to safeguard milk yield. During decades of one-sided selection for milk yield, man has exploited the cow's potential to prioritize mammary energy supply without an equivalent progress in DMI capacity. Consequently, genetic selection for milk yield has widened the gap between energy expenditure and energy intake, and has increased the cow's inclination to respond to energy deficiencies in the transition period by aggressive body tissue breakdown. Chronically elevated concentrations of non-esterified fatty acids and ketone bodies have been demonstrated to affect multiple organ systems including the immune system, the reproductive axis and the liver and are, in contrast to absolute milk yield, closely and consistently related to the final incidence of reproductive disorders. Especially the selection for milk yield and hence the cow's tendency to prioritize mammary energy and glucose supply rather than the actual level of production as such has been named as the main risk factor, This concept is illustrated by the widespread clinical perception that a high-yielding Holstein Friesian cow exposed to a seemingly minor periparturient disorder, such as retained placenta, often succumbs to a persistent catabolic state and the development of more severe disorders, such as ketosis, left displacement of the abomasum or hepatic lipidosis, while a cow of a former more robust, breed would simply reduce energy expenses via milk yield.

Glucose is the molecule that drives milk production in dairy cows. The supply and utilization of glucose are tightly regulated by homeostatic and homeorhetic mechanisms. Insulin plays a pivotal role in the glucose metabolism of dairy cows. The effect of insulin on the glucose metabolism is regulated by the secretion of insulin by the pancreas and the insulin sensitivity of the skeletal muscles, the adipose tissue and the liver. Besides its effect on the glucose metabolism, insulin influences the lipid and protein metabolism as well. A state of insulin resistance may develop as part of physiological (pregnancy and lactation) and pathological processes which may be manifested as decreased insulin sensitivity or decreased insulin responsiveness.

# Factors contributing to immunosuppression in the dairy cow during the periparturient period

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Large improvements have occurred in the production and efficiency of the dairy cow during the last 3 decades. Based on veterinary records, these improvements have unfortunately not been followed by simultaneous improvements in the disease incidence. A large fraction of the disease problems relate to infectious disease during the transition period, defined as $\pm$ 3 weeks relative to parturition. During this transition from late pregnancy to early lactation, most cows experience a period of natural immunosuppression characterized by immune cell dysfunction. In addition, cows mobilize body tissue in order to meet the nutrient demands during early lactation at this time. There has been a growing interest in the relationship between the rate and extent of tissue mobilization and immunosuppression that increases the risk of infectious disease during the periparturient period. This review will focus on the interplay between the metabolism and immune function of the periparturient dairy cow.

Earlier reviews have covered critical periods such as the transition period in the cow and its influence on health and immune function. Knowledge on topics such as the interplay between the endocrine system and the immune system as well as nutrition and immune function is crucial for our understanding of disease risk and our opportunities to prevent diseases. Therefore, to build onto this, our main focus will be on the effect of physiological imbalance on immune function.

To a large extent the health problems during the periparturient period relate to cows having difficulty in adapting to the nutrient demands for lactation. This may result in physiological imbalance, a situation where the regulatory mechanisms are insufficient for the animal to function optimally leading to a high risk of a complex of digestive, metabolic and infectious problems. Metabolism plays a pivotal role in the immune response. The utilization of key nutrients, e.g. fatty acids and glucose, by bovine immune cells has not been fully elucidated and alterations in their availability during the transition period may link physiological imbalance to the risk of infectious disease. This review discusses the complex relationships among metabolic status, individual metabolites and immune function and how these complex interactions increase the risk of disease during early lactation. A special focus will be placed on the major energetic fuels currently known to be used by immune cells (i.e. glucose, non-esterified fatty acids, beta-hydroxybutyrate, and glutamine) and how these fuels and certain metabolic states, such as degree of negative energy balance and risk of physiological imbalance, contribute to immunosuppression during the periparturient period.

# Impact of nutrition and oxidation stress on disease susceptibility in the periparturient period

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Dairy cattle are susceptible to increased incidence and severity of metabolic and infectious diseases during the transition period. Health disorders occurring around the time of calving may greatly impact the productive efficiency of dairy cattle in the ensuing lactation. A major contributing factor to increased health disorders is thought to be alterations in bovine immune mechanisms. Therefore, it is not surprising that considerable research efforts have focused on defining how host immune defenses change as a consequence of the lactation cycle and understanding the factors that may contribute to immune dysfunction during this critical period. Inflammation is an important aspect of the innate immune system that can determine the outcome of several economically important diseases such as mastitis and metritis. An efficient inflammatory response during the early stages of infection, for example, can result in the rapid elimination of pathogens without any noticeable changes to host tissues. Exaggerated inflammatory responses, however, can cause damage to host tissues and contribute significantly to the pathophysiology of disease. Dysfunctional inflammatory responses often occur in transition cows that fail to adapt physiologically to the high-energy demands of lactation and succumb to metabolic stress. Metabolically driven increases in lipid mobilization during times of negative energy balance, for example, can disrupt the delicate balance between the initiation and resolution of inflammatory responses. Increased metabolic activity during early lactation also results in the progressive development of oxidative stress that is thought to be another significant underlying factor leading to dysfunctional inflammatory responses. Nutritional strategies that can reduce intense lipid mobilization and can control the development of oxidative stress may optimize the efficiency of innate defenses and improve the overall health and productivity of transition dairy cattle.

# Subacute ruminal acidosis (SARA) challenge, ruminal condition and cellular immunity in cattle

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Subacute ruminal acidosis (SARA) is characterized by repeated bouts of low ruminal pH. Cows with SARA often develop complications or other diseases, and associate physiologically with immunosuppression and inflammation. Ruminal free lipopolysaccharide (LPS) increases during SARA and translocates into the blood circulation activating an inflammatory response. LPS in the systemic circulation could engage pattern recognition receptors, affecting leukocyte populations and triggering the production of pro-inflammatory cytokines and acute phase proteins. To give an outline of the relationship between ruminal condition and cellular immunity in SARA cattle, the results of our research on the effect of hay feeding in weaning calves, effects of bacteria-based probiotics in SARA and diarrheal calves and changes in ruminal condition and cellular immunity in cattle with repeated induced SARA are referred.

Ruminal fermentation and cellular immunity are encouraged by supplementing hay with calf starter during weaning. SARA calves given a 5-day repeated administration of a bacteria-based probiotic had stable ruminal pH levels (6.6–6.8). The repeated administration of probiotics enhances cellular immune function and encourages recovery from diarrhea in pre-weaning calves. Furthermore, the ruminal fermentation could guard against acute and short-term feeding changes, and changes in the ruminal microbiota composition of SARA cattle might occur following changes in ruminal pH. The repeated bouts of low ruminal pH in SARA cattle might be associated with depression of cellular immunity. Increasing ruminal and systematic LPS levels might be related to cellular immunity in SARA cattle; however, further research is need to reveal the relation between feeding strategy, ruminal condition and cellular immunity.

# Disease prevention in dairy cows through nutrition

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The objective of this presentation is to address the basis for and prevention of feeding- and management-related diseases (*e.g.* fatty liver, ketosis, and rumen acidosis). The large increase in milk yield and the structural changes in the dairy industry have caused major changes in *e.g.* the feeding, management and housing of the dairy cow. The quality of roughage has been increased markedly, the proportion of concentrates has been increased and the diet composition has been balanced to accommodate the needs of the modern dairy cow. However, while large improvements have occurred in production and efficiency, the disease incidence, based on veterinary records, do not seem to be improved.

The majority of the production diseases occur around calving or during early lactation and often the problems are related to inappropriate feeding and/or management during the previous lactation, the dry period or late pregnancy. Inappropriate feeding and/or management may reduce cows' ability to adapt to the nutrient demands for lactation that are believed to be important for a successful transition to lactation.

Unfortunately, few studies have documented prevention strategies for feeding-related diseases and consequently they have been developed based on risk factors and knowledge of the aetiology of the diseases. Strategies to prevent feeding related diseases are therefore based on major factors that directly or indirectly are believed to increase the risk of fatty liver, ketosis, acidosis or any other production disease. Factors such as over-conditioning at calving, excessive mobilisation of body fat, low nutrient intake, nutrient or diet specific factors and management and environmental stress are key elements in preventing feeding-related diseases.

Traditionally prevention strategies for feeding related diseases are carried out at the herd level or at a group level. However, we believe it is difficult to prevent feeding related disease by only focusing on the herd or group level due to the large variability in different physiological parameters such as blood metabolites. Cows that have difficulties in adapting to the nutrient demands for lactation may develop physiological imbalance or subclinical disease states. Cows in physiological imbalance has been defined as cows whose parameters (reflecting the function of the digestive tract, metabolic state and immune state) deviate from the normal, and who consequently have an increased risk of developing production diseases (clinical or subclinical) and reduced production and/or reproduction. It is a major challenge to combat these states that are associated with increased risk of disease and suboptimal performance and reproduction. By their nature these subclinical states are difficult for the farmer or farm staff to identify. However, early detection of physiological imbalance or subclinical states is crucial for proactive risk management in order to prevent risk of disease development and loss of efficiency.

It is argued that proactive risk management needs to be carried out at individual dairy cow level and at real-time to allow proactive management. This calls for easily accessible data or samples, *e.g.* milk that can be collected and analysed automatically in-line and used real-time. Aspects of ideal physiological biomarkers and automated systems are briefly discussed.

# Improvement of reproductive performance with emphasis on transition cow management

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The three largest expenses of the dairy business are: 1) feeding lactating dairy cows, 2) raising replacement heifers, and 3) labor. In practice, however, personnel performance (labor) likely determines the transition management success of lactating cows and replacement heifers. For any dairy operation, calving is an essential requirement of the production system in which cows initiate lactation and provide the future replacements of the herds. Reproductive performance of lactating dairy cows directly influences the annual frequency of calving (which affects the number of replacement heifers available) and milk yield (due to extended low productivity lactation and dry period). Many factors such as feed management (*e.g.*, hypocalcemia), cow comfort (*e.g.*, resting time) of pre-fresh and fresh cows, calving management (*e.g.*, dystocia), metabolic profile (*e.g.*, BHBA, NEFA), uterine diseases (*e.g.*, retained fetal membranes, metritis), pregnancy loss, semen handling, and personnel performance among other affect the conception risk (CR) and 21-day pregnancy rate (PR) of lactating dairy cows. Therefore, best transition cow management practices (during the weeks before and after calving) are key determinant for optimum reproductive performance of cows, economic success, and sustainability of dairy operations. Suboptimal reproductive performance leads to extended days open, increased culling due to reproductive failure, and decreased milk yield. Choosing the most cost-effective reproductive protocol for the specific dairy herd is a critical managerial decision. Every dairy farm is an integrated system and decisions made on one area of the farm will have an impact on other areas of the farm. There are many reproductive tools available, from synchronization of ovulation to estrus detection programs (visual observation or measuring cow activity); but regardless of the tool a farmer may use, proactive management practices at the farm level matter when it comes to reproduction. For instance, resting time (hours lying per day) of close-up and fresh cows is significantly associated with a drop in dry matter intake (DMI). This drop in DMI early in lactation usually leads to the negative energy and calcium balance (*e.g.*, hypocalcemia, ketosis) with the subsequent negative effect on the immune system (*e.g.*, uterine diseases and cysts). There are four key aspects to consider when developing a reproductive program for lactating dairy cows: (1) proportion of lactating cows cycling at the end of the voluntary waiting period; (2) the economic outcome of reproductive programs using estrous detection (ED), timed-AI (TAI), or combination of both; (3) the impact of improving both compliance and accuracy of ED on herd profitability (AI technicians); and (4) identify non-pregnant cows early after insemination and strategies to aggressively re-inseminate open cows. Compliance with each injection of the TAI protocol (*e.g.*, Presynch-Ovsynch) affects reproductive performance (CR and PR) and the subsequent economic benefits. Dairy producers should assess AI technician performance by considering the accuracy of ED and compliance to each injection of the reproductive protocol before implementing or changing programs. Integrating an aggressive and accurate ED and TAI program to re-inseminate cows that spontaneously return to estrus, concurrent with a routine pregnancy diagnosis (32 days after AI) and resynchronization of non-pregnant cows, will improve PR, reduce days open, and increase the overall profit of the herd. Furthermore, designing and implementing a proactive transition cow management program (from feed management, cow comfort, to personnel training) will significantly reduce calving-related diseases, improve uterine environment and ovarian structures (*e.g.*, CL), and optimize reproductive performance of lactating dairy cows and increase profitability of the herd regardless of the reproductive program used.

# Genetic selection of cattle for improved immunity and health

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The immune system is a sensing structure composed of tissues and molecules that are well integrated with the neuroendocrine system. This integrate system ensures non-self from self-discrimination. In this capacity the immune system provides detection and protection from a wide range of pathogens. In mammals, the immune system is regulated by approximately 2000 genes (8–9% of the genome) which indicate its high genetic priority as a critical fitness trait providing survival of the species. Identifying and selectively breeding livestock with the inherent ability to make superior immune responses can reduce disease occurrence, improve milk quality and increase farm profitability. Healthier animals also may be expected to demonstrate improvements in other traits, including reproductive fitness. Using the University of Guelph's patented High Immune Response (**HIR**) technology it is possible to classify animals as high, average, or low responders based on their genetic estimated breeding value (**EBV**) for immune responsiveness. High responders have the inherent ability to produce more balanced and robust immune responses compared with average or low responders. High responders dairy cattle essentially have about one-half the disease occurrence of low responders, and can pass their superior immune response genes on to future generations thereby accumulating health benefits within the dairy herd. The Semex Alliance, Canada's largest dairy genetics company, obtained an exclusive license from the University of Guelph to utilize the HIR procedure to identify sires with the high immune response classification. These sires are designated as *Immunity*＋, marking their enhanced capacity to make protective immune responses. The immune response traits used in establishing HIR EBVs are moderately highly heritable having heritability estimates of approximately 0.25 to 0.35, which is in the same range as those for milk production traits, and well above those for most reproductive traits. To date, we have tested more than 1,000 Holstein sires and dams, and have not seen any substantial negative impact of selecting for enhanced immune response on production or reproduction traits. This indicates that it possible to genetically improve immunity with minor if any impact on other economically important traits. In fact, several beneficial associations occur between immune response and reproductive traits such as calving ease and number of services to conception. Recent studies by our group have also evaluated genomic profiles of high and low immune responders using the *Illumina Bovine SNP50 BeadChip*. In these genome-wide association studies (**GWAS**) antibody-mediated immune responses, as well as cell-mediated immune responses, the two key components of the adaptive immune system, are associated with unique genomic profiles. The significant genomic variation associated with these immune response traits is the first step toward a genomics test, to complement the currently available phenotypic test for immune response as an approach to improve inherent animal health.