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# Molecular and immune mechanisms underlying bovine lameness



## Key external stakeholders:

Dairy farmers, dairy industry, Department of Agriculture, Food and the Marine (DAFM).

## Practical implications for stakeholders:

- Lameness is considered the most serious welfare concern facing the European dairy industry. One of the most serious causes of lameness is damage to the horn of the claw.
- Dairy lameness is primarily caused by diseases or injuries to the hoof, which can be categorised as either affecting the claw horn, or the surrounding skin. Claw horn disorders (CHD; characterised by sole haemorrhages, sole ulcers and white line disease) are non infectious in nature, and result from complex genetic and environmental interactions.

## Main results:

- Cows with claw horn disorders showed a behavioural (locomotor ability) and physiological profile different to healthy cows. The stress hormone, cortisol, was associated with damage to the sole, as was the leukocyte profile (high neutrophil percentage, and low lymphocyte percentage).
- Claw horn damage was also associated with a gene expression profile associated with activation of the immune system. Several genes were identified that appear to be more highly expressed in cows with claw horn damage than in healthy cows.

## Opportunity / Benefit:

The results of this research have

- Demonstrated that lame cows display several behavioural and physiological responses that are representative of a sickness response, indicating a lameness-associated systemic activation of the immune system.
- Demonstrated that as sole haemorrhage score increased (worsened) cows had more impaired locomotion and had higher concentrations of circulating glucose, urea, and haptoglobin.
- Demonstrated that the stress hormone, cortisol, was associated with damage to the sole, as was the leukocyte profile (high neutrophil percentage, and low lymphocyte percentage).
- Demonstrated that several genes are more highly expressed in cows with claw horn damage than in healthy cows and all of the genes that were differentially expressed are associated with general activation of the immune system.

## Collaborating Institutions:

None

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### 1. Project background:

Lameness causes severe pain and distress for the cow and substantial economic losses. Dairy lameness is primarily caused by diseases or injuries to the hoof, which can be categorised as either affecting the claw horn, or the surrounding skin. Claw horn disorders (CHD) are non infectious in nature, and result from complex genetic and environmental interactions. Weakening of connective tissue near the time of calving can also cause the pedal bone to drop and compress the corium, further disrupting claw horn formation. Early and accurate lameness detection means overall prognosis and the welfare of cows is improved. Unfortunately, early detection of lameness and CHD is extremely difficult; cows show little behavioural response to pain until injuries are advanced, and stockpersons find it difficult to detect signs of impaired locomotion. Thus it is unlikely that gait changes alone will provide accurate early detection of lameness caused by CHD, and objective measures to aid lameness diagnosis that can be clinically applied at farm level warrant investigation. Moreover, the prospect of identifying objective biomarkers of inflammatory hoof lesions could help identify animals in need of pain relief and provide appropriate targets for the development and monitoring of novel lameness therapies. Peripheral blood mononuclear cells (PBMCs) are immune cells that can be obtained relatively non-invasively, and are responsible for surveillance of the body with regard to injury and disease. They display specific expression signatures with regard to several diseases in cattle. There is little published information on the physiological and immune differences between healthy cows and cows that have claw horn disorders. This project set about addressing the knowledge gaps.

### 2. Questions addressed by the project:

- Is the physiological and immunological profile of cows that are clinically lame due to the presence of sole ulcers different to that of healthy cows?
- Is the leukocyte gene expression profile of cows that are clinically lame due to the presence of sole ulcers different to that of healthy cows?
- Are the physiological, immune and gene expression profiles of lame cows similar to those of cows that have mild to severe sole haemorrhages?
- Are any changes in measures of physiology and immunity associated with sole ulcers or haemorrhages evident up to three months prior to their development?

### 3. The experimental studies:

1. The objective of the first study was to characterise differences in leukocyte profile, cortisol and DHEA response, metabolite profile, and expression of genes associated with lameness between cows with sole ulcers and sound cows.
2. The second study compared these responses in cows with sole haemorrhages ranging from severe to mild/none.
3. The third study was a retrospective longitudinal study, comparing these responses in cows that had severe sole haemorrhaging approximately three months into the lactation with these measures at calving, and with cows that did not develop sole haemorrhages.

### 4. Main results:

- Using conventional blood indicators of stress (i.e physiological, haematological and immunological variables), cows with sole ulcers were shown to be in a state of physiological stress compared with healthy cows.
- Through the use of molecular techniques (i.e. real-time (RT)-qPCR and next generation sequencing technology), we identified a number of key genes regulating immune function the expression of which was different in cows that had sole ulcers compared with healthy cows. Up- or down-regulation of this function of these genes could have a profound impact on the health of cows in terms of susceptibility to infection during a lameness episode.

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- An increase in (worsening of) sole haemorrhage score was associated with impaired locomotion, increased levels of circulating metabolites and stress hormones, and a leukocyte profile associated with stress, thus indicating that horn damage not as severe as ulceration can cause systemic changes that could increase susceptibility to illness.
- An increase of sole haemorrhage scores was also associated with changes in gene expression indicative of physiological stress and changes in immune activation.
- We found no indication of any changes in metabolite or immune profile 2 – 3 months prior to sole damage that could be used as indicators of a risk of developing sole haemorrhages.

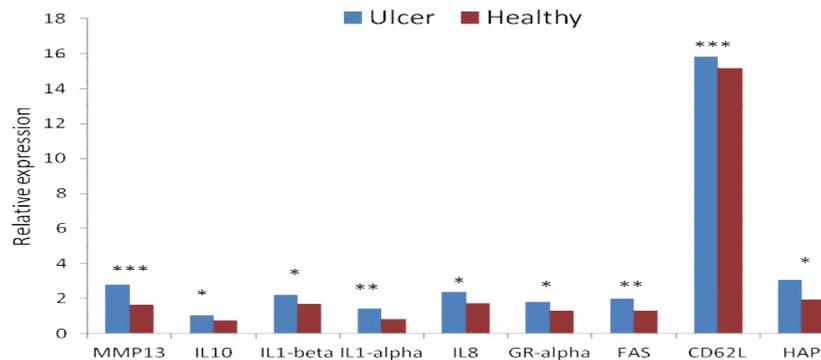


Figure 1. Differences in gene expression in white blood cells of cows that either had an ulcer or were otherwise healthy. \* indicates means differ by  $P < 0.1$ , \*\* by  $P < 0.05$  and \*\*\* by  $P < 0.01$ .

#### 5. Opportunity/Benefit:

The results of this research have; 1) demonstrated that cows that have sole ulcers have alterations in their immune system that could increase susceptibility to disease; and 2) demonstrated that even a more mild form of damage, i.e. sole haemorrhaging, which does not cause clinical lameness, results in alterations to the cows' gait and similar changes to the metabolic and immune profile.

#### 6. Dissemination:

##### Main publications:

- O'Driscoll, K. and Earley, B. (2012) 'Leukocyte profiles of cows with claw horn disorders.' *Proceedings of the ADSA/ASAS Joint Annual Meeting*, Phoenix, Arizona, USA, 15-19 July.
- O'Driscoll, K. and Earley, B. (2012) 'Leukocyte profiles of cows with claw horn disorders.' *Proceedings of the Agricultural Research Forum*, Tullamore, Ireland, 12-13 March.
- O'Driscoll, K., Olmos-Antillon, G., Llamas Moya, S., Mee, J.F. Earley, B., Gleeson, D., O'Brien, B. and Boyle, L. (2012) 'A reduction in milking frequency and plane of nutrition improves dairy cow immune status.' *Journal of Dairy Science* 95 (3) 1177-1187.

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