This month's issue features: training for lactose digestion, breast size and milk supply, protection against cow's milk allergy with probiotics, and highlights from 2015 IMGC symposium.

**Highlights from the 2015 IMGC Symposium**

The 12th International Milk Genomics and Human Health Symposium concluded Wednesday (28 Oct). This year the symposium returned to Sydney, Australia, where it was last held seven years ago. Comparing this year's program and the program from 2008, I was struck by how the symposium has evolved, and certainly how the genomics of milk science has developed. Here are some of the main themes and findings:

1) As has become our tradition, the program opened with a stimulating overview of the exciting milk science and genomics research findings both past and present from Bruce German. Danielle Lemay followed with highlights from SPLASH! milk science update, and foreshadowed future topics. SPLASH! continues to expand its reach, with over 80,000 hits in the past year. The tone and pace of the symposium was set to go!

2) The symposium covered many topics, such as the nutritional and metabolic factors that affect mammary gland development and milk production. The influence of such factors on neonatal and lifetime health of the offspring was another subject of the meeting (Brand-Miller, Tellam, Rijnkels, Williamson, Elwood). The quality of nutrition and metabolic control in the mother during pregnancy clearly affects body composition in the newborn. There is a great deal of evidence that links these measures to health. Animal models are proving useful to explore the genomic mechanisms underlying these effects. Epigenetic marks, or chemical modifications that determine levels of gene expression, show complicated patterns of response to, for example, over nutrition during pregnancy. Different “programs” of genomic modification may account for subtle changes that, collectively, make an enormous difference to health or milk production.

3) A number of research presentations explored the theme of post genome-prediction phenotypes (Clark, Thomson, Abelsayed, Gregsen, Wang, Rochfort). Reflecting the consensus of his innovative dairy farmer team, Cameron Clark outlined the virtuous cycle of innovation and implementation of new advances. The rapid advances being developed in farm system management and instrumentation have delivered remarkable tools for measuring continuous and/or incredibly detailed phenotypes. The symposium presentations from these scientists provided striking examples showing the challenges of distilling the amount of data generated by these tools to interpret and apply the information they contain. As scientists, we recognize the inherent value of data collection, but we cannot possibly bury farmers with the weight and volume of data we can now so readily collect. One priority test for what to extract, says Clark and his farmer team, is the “so what” filter. Unless we can explain the value to farmers at the outset, it lacks purpose.

4) Symposium attendees were presented with elegant approaches to distilling large data sets from our statistician and geneticist colleagues (Thomson, Abelsayed, Reverter, Gregerson, Wang). They demonstrated how to turn complex biological data into parameters that constitute novel phenotypes, such as dam-offspring measures, extended lactation curves, health and welfare records, milk processing quality, and cow physiological data. Their approaches fit neatly into current herd improvement systems, showing how new and meaningful complex phenotypes could be integrated into state-of-the-art genomic selection criteria. However, they emphasized the necessity to use the most appropriate reference populations when incorporating phenotypic data for calculating genomic breeding values.

5) Milk oligosaccharides were once again an area of abiding interest (Frese, Sanctuary, Wang-B), but an analysis of milk lipids was also presented in this context (MacGibbon). Consumption of milk and milk-derived constituents affects the nexus between gut, immunity, brain, and health. Oligosaccharides in milk have apparently evolved to pair with healthy
commensal microbes to prime healthy gut development. The complex subject of cognition in children and the challenges presented by pre-term birth are also an area of increasing research effort.

6) Gut microbiota is fundamental to a healthy start in life, but the use of milk constituents to modulate gut health can potentially impact a range of other outcomes. Symposium attendees heard evidence of milk oligosaccharides and milk exosomes reducing inflammation in animal models of arthritis (Stahl, van der Loo). Milk constituents have a modulating effect at the cellular level and promote balance in the immune system. Another related area is the intriguing question of whether milk miRNA, which is a feature of milk across diverse species of mammals and even monotremes (platypus and echidna), has a specific role (Gillespie, LeFevre). Probiotics based on the milk-selected commensal bacteria and their possible interactions with miRNA are also emerging in health promoting products (Simpson-M, Demers-Mathieu). A comparative analysis of protein digestion into bioactive peptides, using peptide analysis of human and bovine milk, documented the potential range of antimicrobials and other potential bioactives. The use of highly sensitive mass spectrometry instruments captured and identified these peptides in microliter volumes of pre-mature baby stomachs, helping to understand their importance (Dallas).

7) The meeting concluded with an elegant expose on the emerging paradigm of nutritional impact based on macronutrient balance (Simpson-S, Raubenheimer). A wealth of data from laboratory and field studies, and across species as diverse as flies and orangutans, was presented to support the Protein Leverage Hypothesis. Protein emerges as the primary driver of dietary choice and calorie intake. The evidence points to a wide-ranging impact of dietary protein on appetite, metabolism, longevity, and reproductive fitness, amongst others. The implications for the consumption of milks of different species, and for formulations based primarily on cow's milk were a lively and fascinating point of discussion.

Once again, an enjoyable social program complemented the scientific program. The highlight was the traditional harbor cruise—always a wonderful way to view the iconic sites of Sydney. The symposium was diverse, informative, and invigorating. Personally, I find that it challenges the mind and sustains the enthusiasm for more of the wonderful multidisciplinary world of milk genomics and human health research. In conclusion, I would like to thank the IMGC sustaining members and sponsors, all those who contributed, and a special thanks to Laurie Jacobson and Gonca Pasin for terrific and generous support.

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Training Your Body to Digest Lactose

- People who are poor at digesting lactose may be able to improve their tolerance of dairy products by consuming small quantities of milk or lactose supplements regularly.
- Only a few, small-scale trials in humans have tested this theory, but the results are encouraging.
- The good news for those who wish to try this approach is that the daily lactose dose needed to see results might be lower than what prompts the symptoms of lactose intolerance.

The common understanding of the inability to properly digest lactose is that it’s all about genetics: either a particular gene in cells lining your upper intestine—which enables everyone to digest lactose as an infant—becomes inactive as you grow up, or it doesn’t. But the truth is less cut and dry. In fact, there is some recent and gathering evidence to suggest that those who suffer the symptoms of lactose intolerance could be better off by frequently consuming small quantities of the sugar that bothers them.

Theoretically, there should be more than one way of making lactose-intolerant people more lactose-tolerant. One option would be to induce production of lactase, the enzyme that digests lactose, in the cells where it has ceased. But this does not appear to be possible in humans (yet). Instead, the method that Andrew Szilagyi, a gastroenterologist at McGill University, in Quebec, Canada, described in a recent paper [1] involves meddling with the composition of bacteria in the latter stages of the gut.
Szilagyi's suggestion is simple. Most lactose-intolerant folk avoid dairy, and therefore have somewhat different populations of gut bacteria to lactose-tolerant people. Thus, he thinks that if the lactose-intolerant were to regularly consume small quantities of the sugar that causes them problems, they could gradually improve their tolerance to it over time. This would alter the composition of the bacteria in their guts, such that it more closely resembles that of lactose-tolerant people.

While this sounds plausible, it is worth noting that the mechanistic details of why it might work are poorly understood. Although it has been established that habitual dairy consumption alters colonic bacteria [2], the details of the changes in species composition and the consequential shifts in the extent of lactose breakdown in different parts of the gut are not thoroughly elucidated.

Nonetheless, the supporting data for this approach is convincing, if limited in its volume. For example, back in 1996, 20 people, with various ethnic backgrounds, and who were all poor at digesting lactose, were randomly assigned to take either a small dose of lactose or one of dextrose, a different sugar, for 10 days [3]. After that initial stage, the 20 participants then switched to the sugar they had not yet taken for an additional 10 days. None of them knew which sugar they were taking at any time.

The trial was run by Steven Hertzler, who now works at Abbott Nutrition, and Dennis Savaiano, who is based at Purdue University, in West Lafayette, Indiana. After completing each of the two 10-day courses, the lactose tolerance of each individual in the trial was tested by giving them a large dose of lactose and recording their subsequent flatulence, diarrhea, abdominal pain—and, more formally, their hourly performance on a hydrogen breath test over eight hours. Encouraging, the course of small lactose doses did improve tolerance: after the 10-day course of lactose, the lactose challenge produced much less hydrogen in the breath compared to after the 10-day course of dextrose. Similarly, ‘hourly rectal gas passages’ and ‘severity’ of flatulence (rated on a five-point scale) were much lower.

Elsewhere in the academic literature there’s the anecdotal case of a 32-year-old man from Sicily who had a perfectly normal score on the hydrogen test before he gave up all forms of dairy for three weeks. When he retook the test, after that period, he showed much higher levels of hydrogen in his breath [4]. As with the 20 volunteers, the suggestion is that the change was caused by a shift in the populations of bacterial species in his gut.

Animal studies back up this interpretation. Recent data from studies in pigs [5] and rats [6] link the feeding of lactose to shifts in the animals' gut bacteria. In rats, for example, metabolic shifts in the bacteria in the part of the gut from which lactose-intolerance symptoms are known to emerge, have been detected as quickly as five hours after lactose consumption. In other words, each meal they eat is shaping the microflora in their innards.

There is the question of how unpleasant the process of becoming more lactose tolerant is likely to be. There, the good news is that it might not be unpleasant at all. The US National Institutes of Health has concluded that most lactase non-persistent people can handle 12g of lactose without noticing symptoms. And the hydrogen breath test does not turn positive until 6g has been consumed. Szilagyi therefore suggests ‘training’ with 5g of lactose per day, based on studies of similar training exercises with another sugar, oligofructose. To put that into perspective, there are 5g of lactose in 100ml, or about a half cup of milk.

Szilagyi also argues that there would be broader health benefits to training, aside from a reduction in the symptoms of lactose intolerance. If people who otherwise don’t consume dairy are newly able to eat it, their risks of developing many diseases should decrease. For example, the odds of getting many cancers decrease, among them colorectal, stomach, breast, and pancreatic cancers [1]. Dairy consumers are also at lower risk of developing Crohn’s disease. Counter-intuitively, a bit less than half a glass of milk a day may be just what the lactose intolerant need.

Do Larger Breasts Make More Milk?

- Low milk supply is one of the reasons many women stop or cannot breastfeed, but does breast size influence their milk production?
- Research shows that milk production is actually compromised in overweight and obese mothers, who often have larger breasts. This suggests that size does not correlate with milk supply.
- Mothers with high body mass index often have less milk-making tissue inside their breasts, which explains the lower than normal milk production in overweight and obese mothers.
- Lower milk supply is also often seen in mothers who give birth preterm.
- These new findings improve our understanding of low milk supply, which could provide new avenues for personalized management of this issue and improve mothers’ breastfeeding success.

Large breasts are often considered more attractive, but how about their function as organs destined to produce milk for the nourishment of the baby? During pregnancy and, particularly during lactation, women are mostly interested in their breasts as sources of food and growth signals for their baby. But, especially among women with breastfeeding difficulties, it is common for women to wonder, “If I had larger breasts, would I produce more milk?”

Milk supply is the ability of a mother’s breasts to produce sufficient quantities of human milk for the baby. Low milk supply is one of the major reasons why women are discouraged to breastfeed and cease breastfeeding early [1], which has potential detrimental effects for both the mother and the baby.

Breastfeeding is known to provide important benefits for both the baby and the mother. Human milk is a live fluid, containing nutrients and biologically active ingredients, such as hormones and stem cells, essential for the baby’s growth and development. At the same time, human milk delivers microbial protection and the immunity that the mother’s body has acquired during her life [2-4]. Amazingly, the mother’s health is also improved from breastfeeding; it actually can protect the mother against breast and ovarian cancer [5], and improve her cardiovascular and metabolic health. The frustration of not being able to breastfeed is therefore understandable, and warrants further investigation.

A number of factors associated with low milk supply have been identified, such as nipple pain, ineffective nursing, hormonal disorders, breast surgery, certain medications, and maternal obesity. Yet, no effective remedies exist because the actual causes of low milk supply at the molecular level inside a breast’s epithelial tissue are still unknown.

And rightly, the notion exists that women with larger breasts can produce more milk and vice versa. But, is this the case? Research into breast size and milk production shows that milk supply is not dependent on breast size, but rather on the amount of epithelial tissue contained in a breast that is capable of making milk [6].

Various studies have associated mother’s body size with low milk supply and reduced breastfeeding rates and duration. This association remains significant even after considering maternal smoking, age, number of births, and other socioeconomic factors [7-10]. Obese mothers often have large breasts, which sometimes are too large for the baby to properly attach to the nipple, resulting in low breastfeeding success [11]. However, in addition to baby attachment issues, accumulating evidence shows that a major factor preventing overweight and obese mothers to breastfeed is the inability of their breast epithelial cells to start producing copious amounts of milk after birth [7, 8]. This is often referred to as unsuccessful initiation of lactation.
But what prevents initiation of lactation in these women despite the fact that many of them have large breasts, which could be perceived as high ability to produce milk? Looking inside a woman’s breasts is not an easy task, especially during pregnancy and lactation, because this requires a biopsy, which is a rather invasive procedure. To overcome this difficulty, a recent study took advantage of breast epithelial cells non-invasively isolated from human milk [12]. In these cells, certain genes are turned on, which enable the cells to gradually make milk as the breast matures during pregnancy, and then deliver it to the baby during breastfeeding.

The study reported a negative association between maternal BMI (body mass index), and the function of a gene that represents the milk-producing cells [12]. This suggested that the breast epithelial tissue is not as mature and ready to make copious amounts of milk in mothers with higher BMI. Most likely, the large breasts of overweight or obese mothers contain more fat cells than milk-making cells, which can explain the low milk supply of many of these mothers [13].

Therefore, breast size does not necessarily translate to more milk-producing cells or higher ability to make milk. Interestingly, the change in breast size (breast volume) from pre-pregnancy to lactation can be an indicator of how well the breast performs during lactation; in other words, how much the milk-producing tissue in the breast grew during pregnancy may predict its ability to make milk [12].

And, in addition to maintaining a normal weight, it seems that a full term pregnancy is important in reaching this ability. The same study reported that the closer a baby was born to term, the better developed the breast of its mother was in terms of its ability to make milk [12]. A number of women giving birth preterm have insufficient milk supply and compromised lactation [14]. Ongoing research is further investigating the molecular causes of this issue, which may help develop management avenues to improve breastfeeding for these mothers and their babies.

The milk-making ability of the breast is an inherent property that fulfills its purpose to nourish the baby. Indeed, the only time during the life of a woman when her breasts reach their full functional maturation is during lactation. This further signifies the uniqueness of this organ, and calls for further investigations of its biology, as well as its pathologies, such as low milk supply. Understanding the molecular mechanisms that govern normal milk synthesis will provide important insight into what goes wrong in mothers that are unable to produce sufficient quantities of human milk for their babies. Larger does not necessarily mean better—quality is superior to quantity.

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How Probiotic Bacteria Protect Against Allergy to Cow’s Milk

- Allergy to cow’s milk is one of the most common food allergies in young children.
- The probiotic bacteria Lactobacillus rhamnosus GG have been shown to be effective in treating cow’s milk allergy, but how they do so is unclear.
- A new study finds that when infants were given L. rhamnosus GG, those who became tolerant to their allergy had very different gut bacteria than those who remained allergic to cow’s milk.
• In particular, infants who developed tolerance had higher levels of bacteria that produce the fatty acid butyrate, which is known to help maintain a healthy gut.

• Follow-up studies could help identify bacterial strains that serve as more effective treatments against food allergies.

Whether it’s to nuts, cow’s milk, eggs, or some other food, food allergies have become increasingly common in recent decades (1–4). Allergy to cow’s milk is especially common, affecting up to 3% of children worldwide (5). There have been many recent efforts to treat cow’s milk allergy, and probiotics have looked particularly promising. Recent studies have shown that feeding infants formula supplemented with the probiotic Lactobacillus rhamnosus GG (LGG) results in higher rates of tolerance to cow’s milk compared to infants fed unsupplemented formula (6,7).

In a new study, researchers from the University of Naples and the University of Chicago found that infants who developed tolerance to cow’s milk allergy after treatment with LGG-supplemented formula had significantly different gut bacteria from those who remain allergic (8). They compared bacteria in stool samples collected from healthy infants, infants with cow’s milk allergy who had been fed LGG-supplemented formula, and those fed formula without probiotics. “What we were surprised about was that we were able to so specifically see that children treated that didn’t gain tolerance had a very different microbial genetic profile,” says Jack Gilbert, a microbial ecologist at the University of Chicago and Argonne National Laboratory, and one of the co-authors of the study. “So it looks like you have to have the right kinds of bugs already in you, and then if you have them in you then you can benefit from that treatment,” he says.

The children who developed tolerance had higher levels of bacteria that produce the fatty acid butyrate, which is known to be helpful for maintaining a healthy gut (9). “The fact that this probiotic expands the abundance of these butyrate-producing bacteria in the gut of children who have those bacterial organisms already present is brilliant,” says Gilbert. “The key element of this work is that we had no idea why the treatment of patients with that particular probiotic organism had any efficacy at all, because the organism appeared to not remain resident in the gut,” he says. “Yet for some reason treatment with that probiotic had an impact on the induction of tolerance, so that was an enigma,” he says.

The findings could help develop more effective probiotic treatments against cow’s milk allergy, says Gilbert. Similar treatments may eventually help with other allergies as well, although this will require a lot more work, he says. “We believe that having the right kind of bacteria in your body in the right place may be highly effective in treating these conditions,” Gilbert says.

Gilbert and his colleagues are planning to test the influence of different butyrate-producing bacteria on allergic tolerance in mouse models. “We might not even need the treatment with the L. rhamnosus probiotic, we might just be able to give them the bacterial probiotic of the organisms which we think are responsible for inducing tolerance,” Gilbert says. “It’s quite possible that just the addition of that one organism will affect the animal’s or human’s tolerance acquisition,” he says.

The researchers will eventually test the effectiveness of these probiotic treatments in humans. “We should be able to move into clinical trials within one to two years,” Gilbert says. Once researchers identify bacterial species that are particularly effective at treating allergies, they could be added to formula or in a food to be used as therapeutics, he says. “We’re getting close to the point where we think we understand the right kinds of organisms to add,” Gilbert says.

“We already know that the addition of probiotics helps children,” Gilbert says. “We think if we can figure out which probiotics to add to boost their system more effectively, then we’ll have a much more effective treatment,” he says.


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