Novel Strategies to Manage the Impact of Unnecessary Feed-induced Immune Responses on Broiler Performance

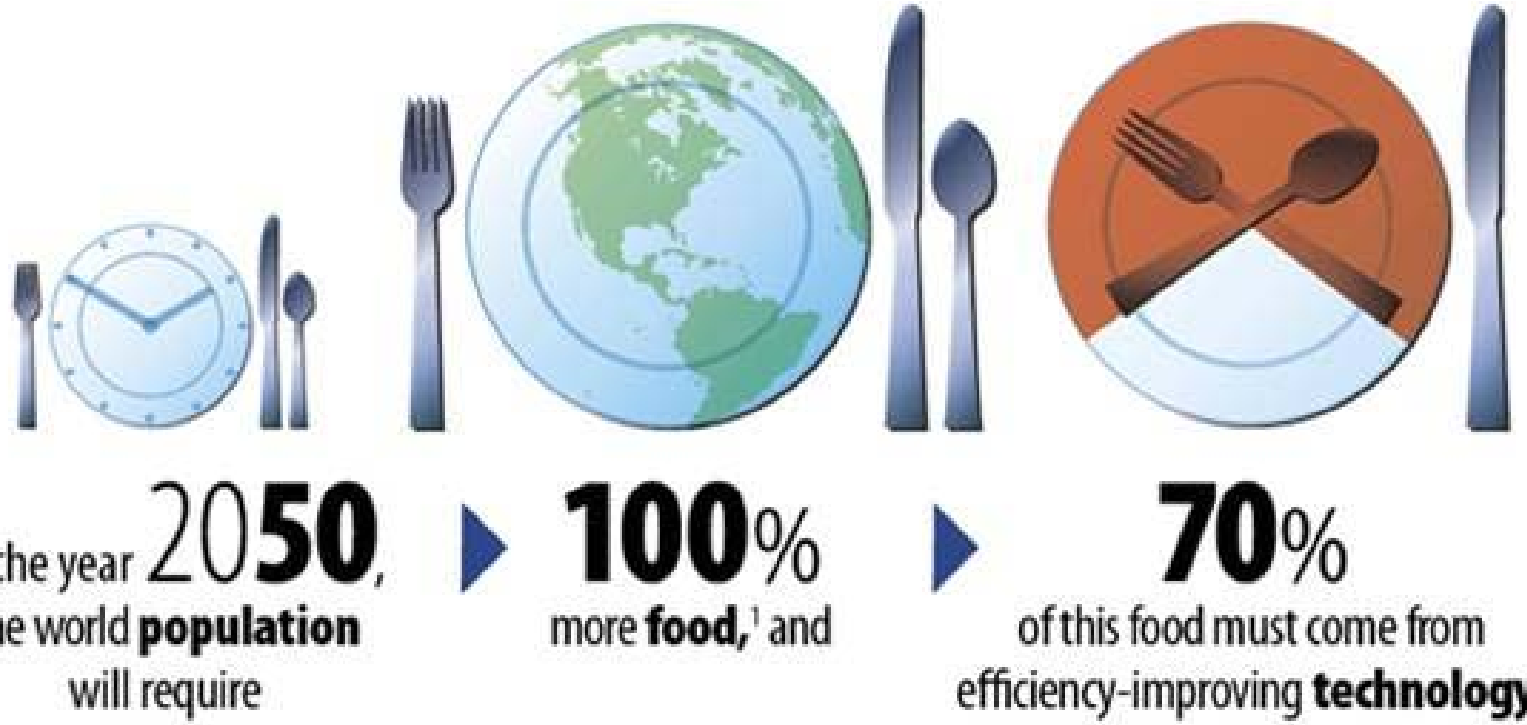
Marco A. Martinez Cummer, Ph.D.

Global Poultry Nutrition Advisor

Elanco Animal Health

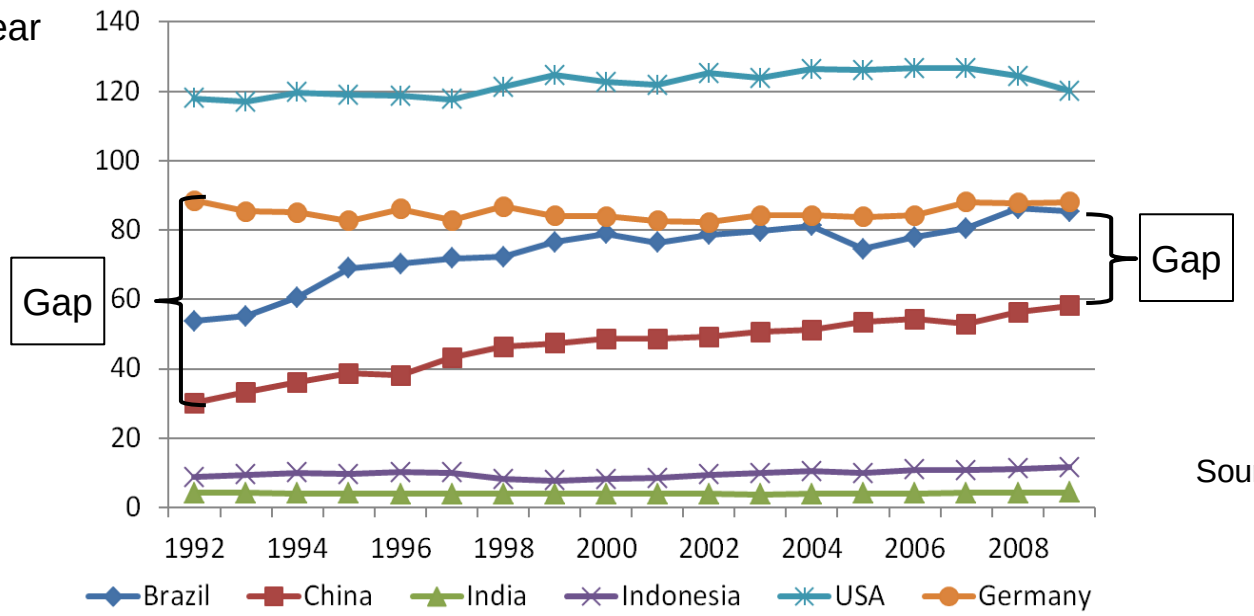


Access to Food- No. 1 Challenge for the next 40 years [21].



21. Simmons, J. Technology´s Role in the 21st Century: Food Economics and Consumer Choice. Elanco Animal Health Newsletter March 2009.

Meat Consumption Gap is Declining![22]



Source: FAOSTAT

- Brazil
  - reached Germany consumption habits
  - Increased meat demand due to increased consumption per capita and increased population
- China
  - will reach Germany consumption habits within the next 10 years
  - Increased meat demand due to increased consumption per capita and increased population
- India and Indonesia
  - Meat demand increase due to human population growth and (so far) NOT due to change in consumption habits

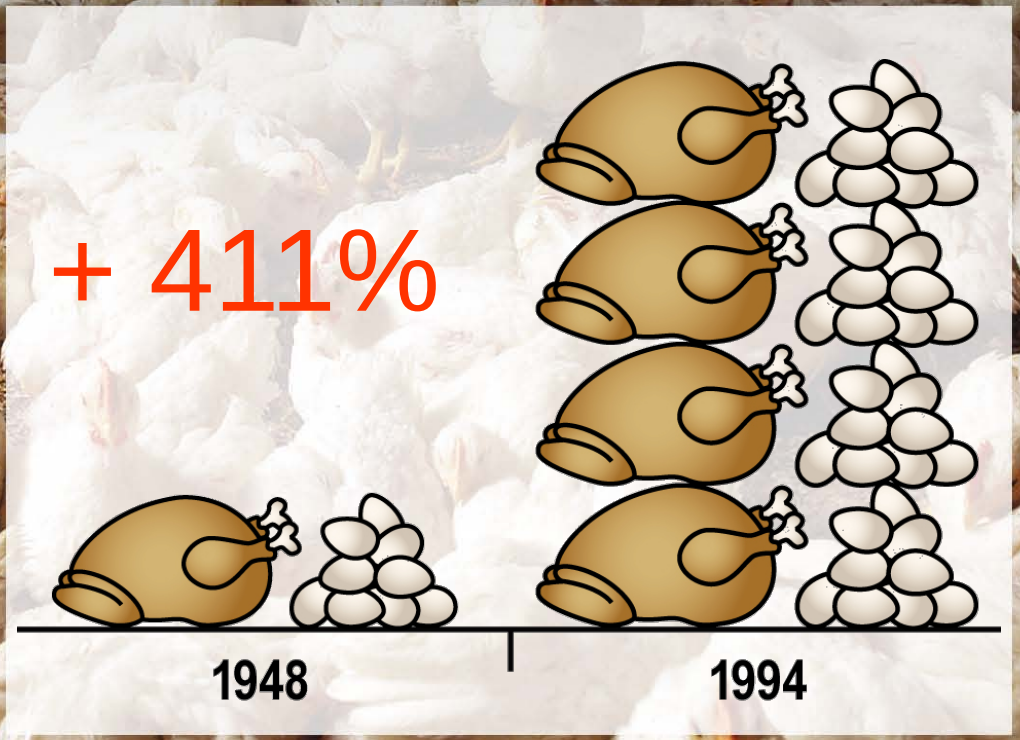


The FAO considers Technology as the key answer to cover 70% of the global food needs by the mid 21st century [21, 22].

Technology…
Something we´ve been using for some time….


In the poultry industry
Elanco

Between 1948-2008, technology helped broiler and egg producers increase production by 411% [20,23].



23. Banerjee, C. Market Analysis for Terrestrial Application of Advanced Bio-Regenerative Modules: Prospects for Vertical Farming. MSc. Disseration, Hohen Landwirtschaftlichen Fakultät der Rheinische Friederichs-Wilhelms-Universität zu Bonn July, 2012.

20. Havenstein, G., Ferket, P. and Qureshi, M. 2003. "Carcass Composition and Yield of 1957 Versus 2001 Broilers When Fed Representative 1957 And 2001 Broiler Diets." Poultry Sci. 82: 1509-1518.

Pressing issues in commercial broiler production[19,22,23].

- Welfare, Reduced use of antibiotics… key topics of increasing importance.

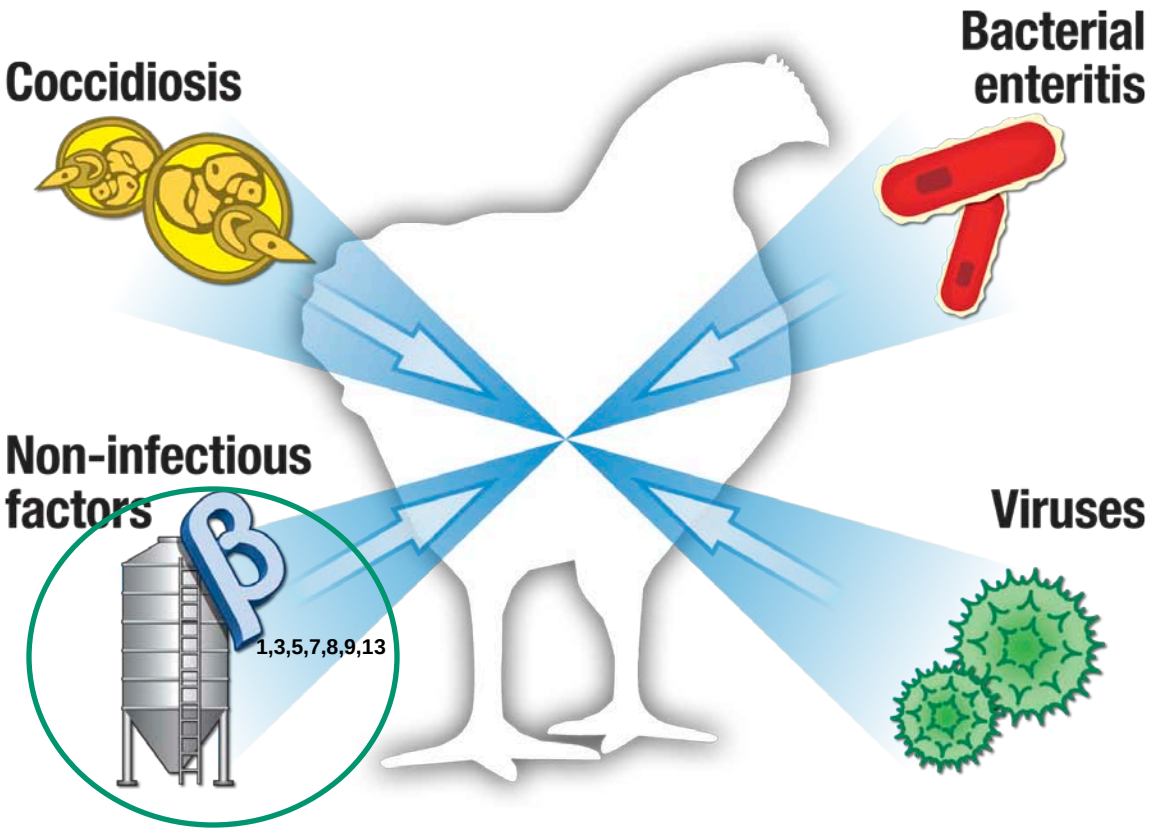
- Healing capacity, after a disease or an immune challenge (infectious or non infectious), is limiting as time passes (earlier slaughtering age).

- Disease & immune activation: Situations to avoid (welfare and profitability).

Intestinal Health and Avian Immunity in the Modern Commercial Broiler[10,11,14].

Elanco

Intestinal Health: 4 triggers



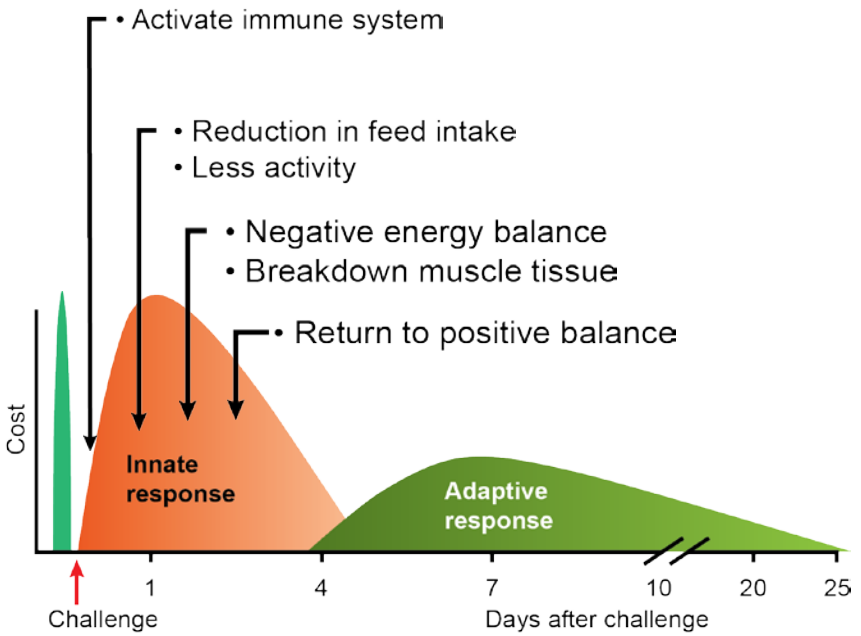
1. Hsiao, H-Y., Anderson, D. and Dale, N. 2006. "Levels of β-mannan in Soybean Meal." Poultry Sci. 85: 1430-1432.
3. Whistler, R. and Saarnio, J. 1957. "Galactomannan From Soy Bean Hulls." J. Am. Chem. Soc. 79: 6055-6057.
5. Stahl, P.D. and Ezekowitz, R.A. 1998. "The mannose receptor is a pattern recognition receptor involved in host defense." Curr Opin Immunol. Feb; 10(1):50-5.
7. Didierlaurent, A., Simonet, M. and Sirard, J-C. 2005. "Innate and acquired plasticity of the intestinal immune system." Cellular and Molecular Life Sciences. 62: 1285-1287.
8. Spurlock, M. 1997. "Regulation of metabolism and growth during immune challenge: an overview of cytokine function." J. Anim. Sci. 75: 1773-1783.
9. Gabler, N. and Spurlock, M. 2008. "Integrating the immune system with the regulation of growth and efficiency." J. Anim. Sci. 86: E64-E74.
13. Anderson, D., Mathis, G., Jackson, M. and Hsiao, H-Y. 2006. "Effect of β-mannanase (Hemicell® Feed Enzyme) on Acute Phase Protein

Avian immune system: overview

- Immune system is a **costly 'organ'**:
  - 2% to 4% for maintenance
  - Much more when engaged and stimulated
- To maximize production, immune system must be:
  - Vigilantly maintained
  - **Activated only when necessary**
- Once activated, a rapid solution or transition from innate system to adaptive system is required to minimize loss of productivity
- **The immune system has a high rank** compared to lean tissue on nutrient demand

3 defense lines

Physical barriers Innate response Adaptive response

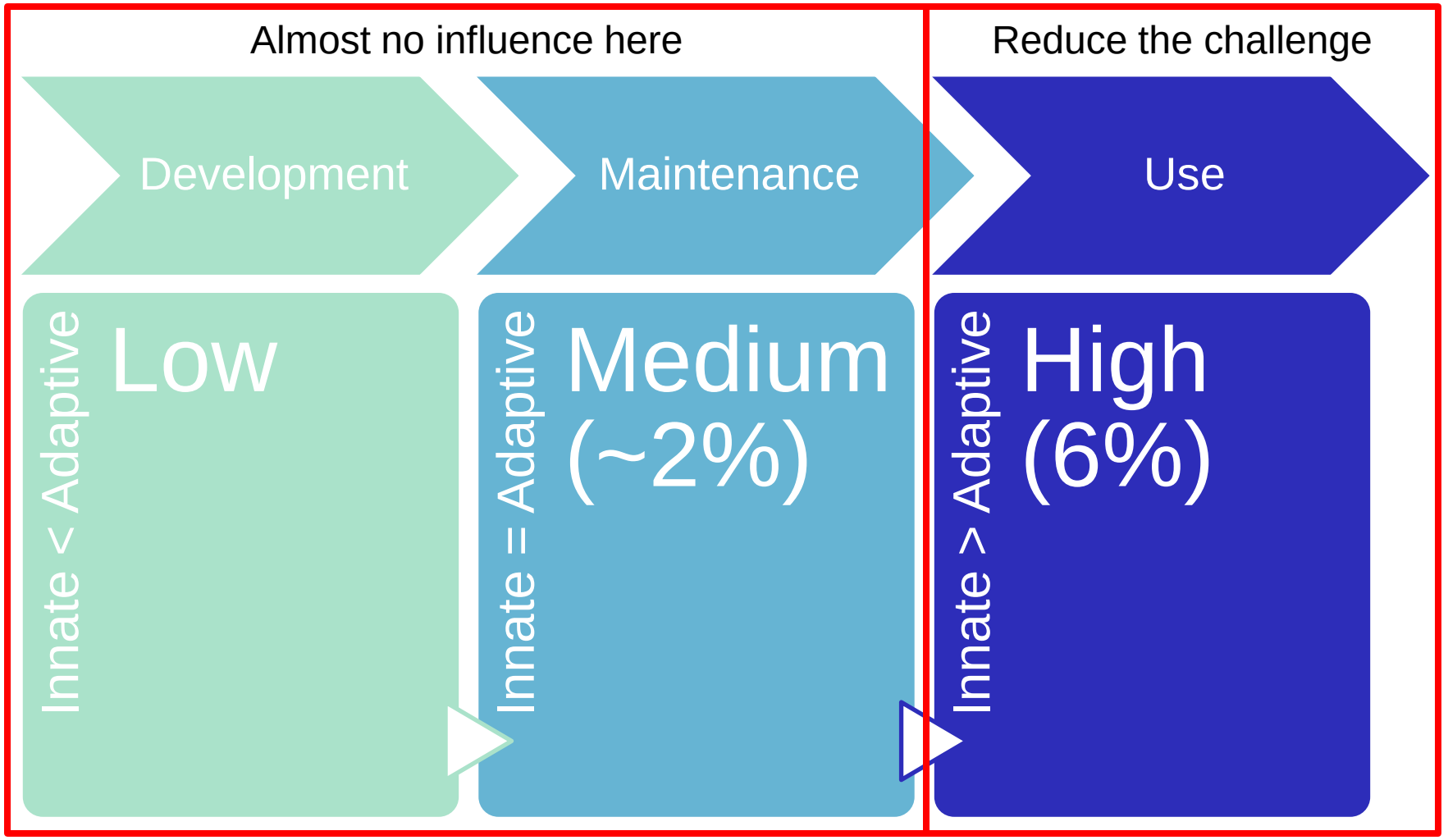


The timing of resource use for the innate system and the adaptive system are very different

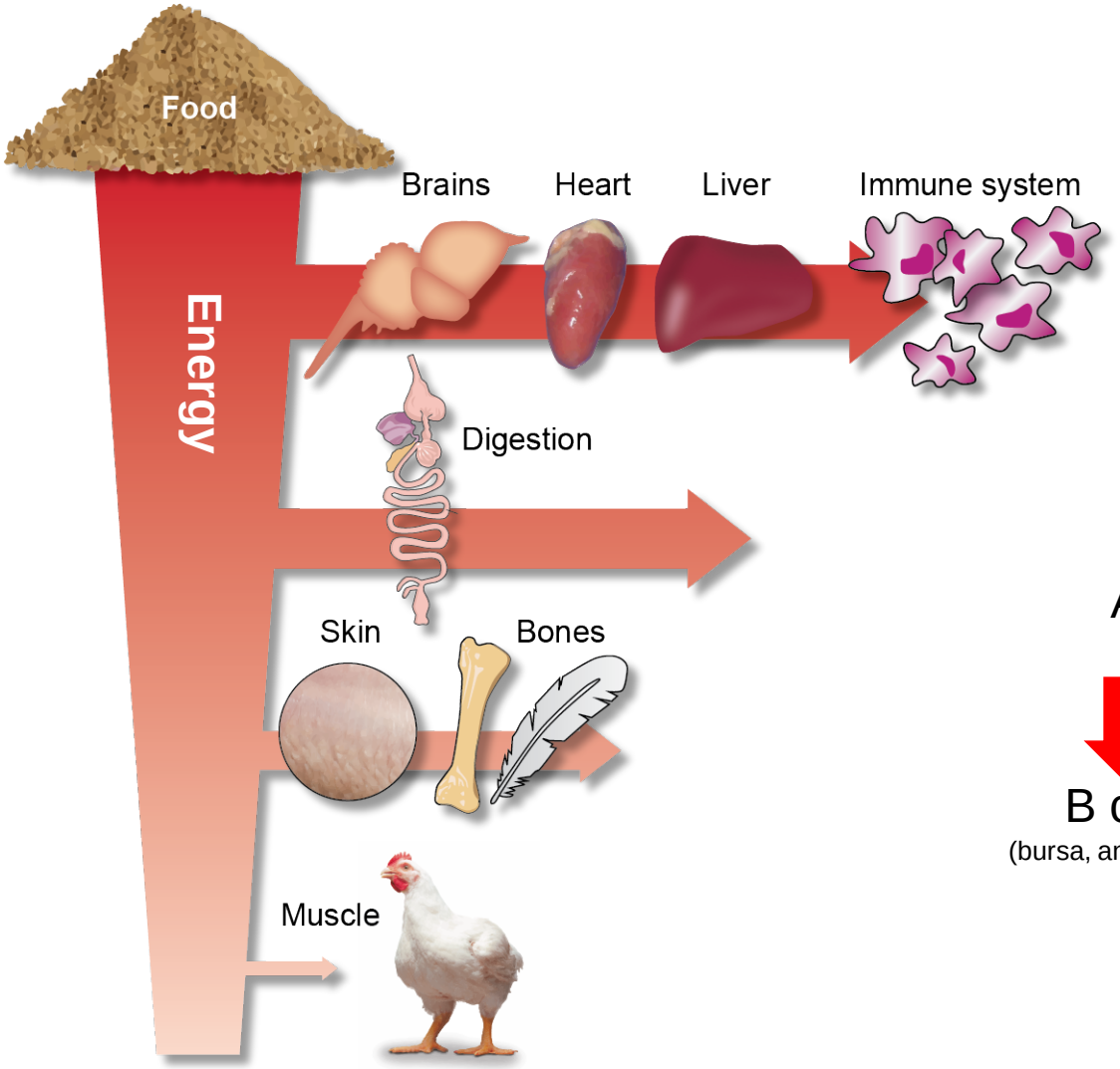
11. Klasing, K. 2007. "Nutrition and the immune system." Br. Poult. Sci. 48(5): 525-537.

How expensive is immunity?

How expensive is immunity?[16]



Mobilization & priority for nutrients[9,11]



Physical barriers
(skin, mucosa, mucus , etc.)

Innate immune system
(macrophages, dendritic cells, APP, etc.)

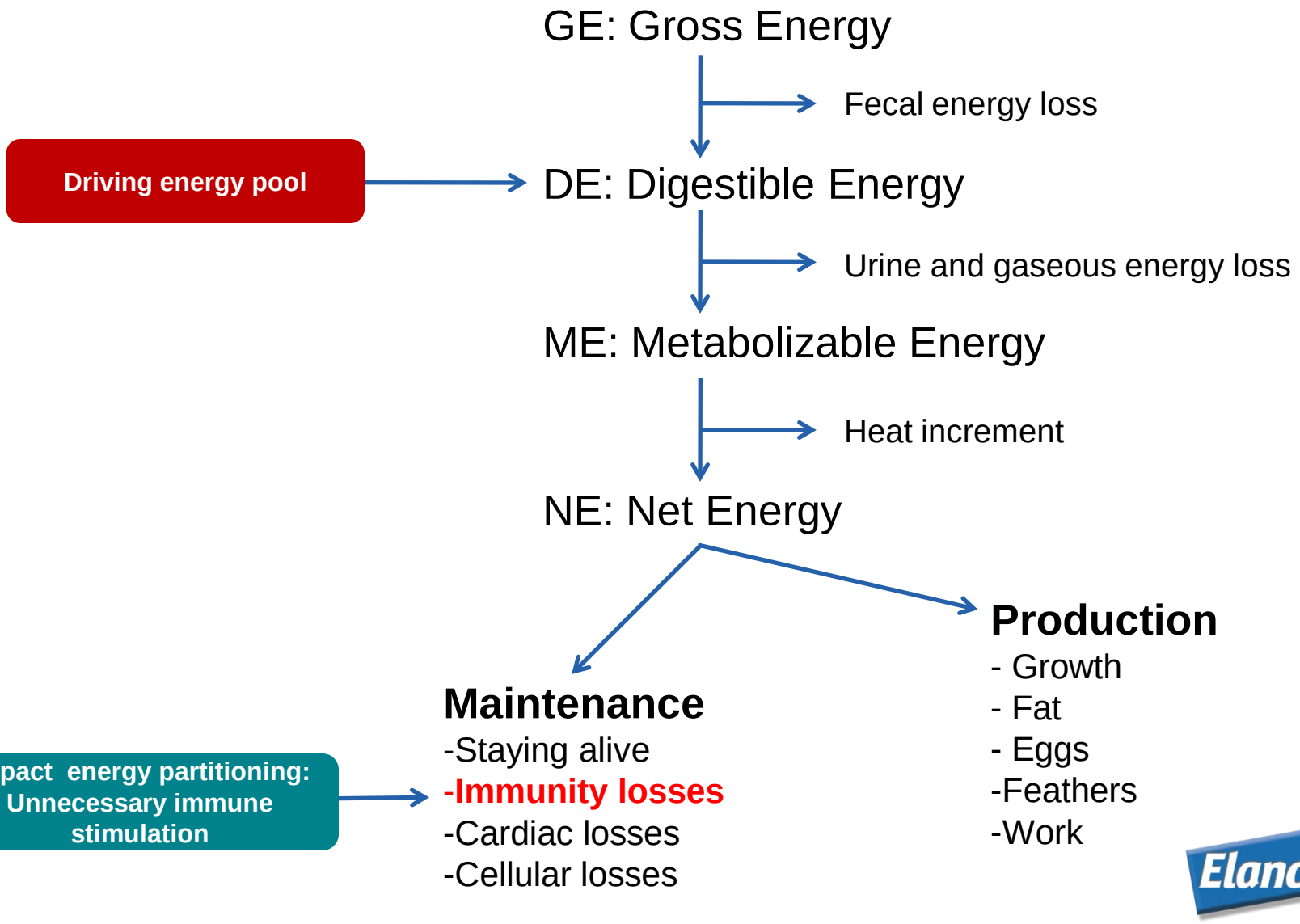
Adaptive immune system
(lymphocytes)

B cells
(bursa, antibodies, etc.)

T cells
(thymus, lymphocytes T, etc.)

11. Klasing, K. 2007. "Nutrition and the immune system." Br. Poult. Sci. 48(5): 525-537.

Key leverage points for driving energy towards growth[24]

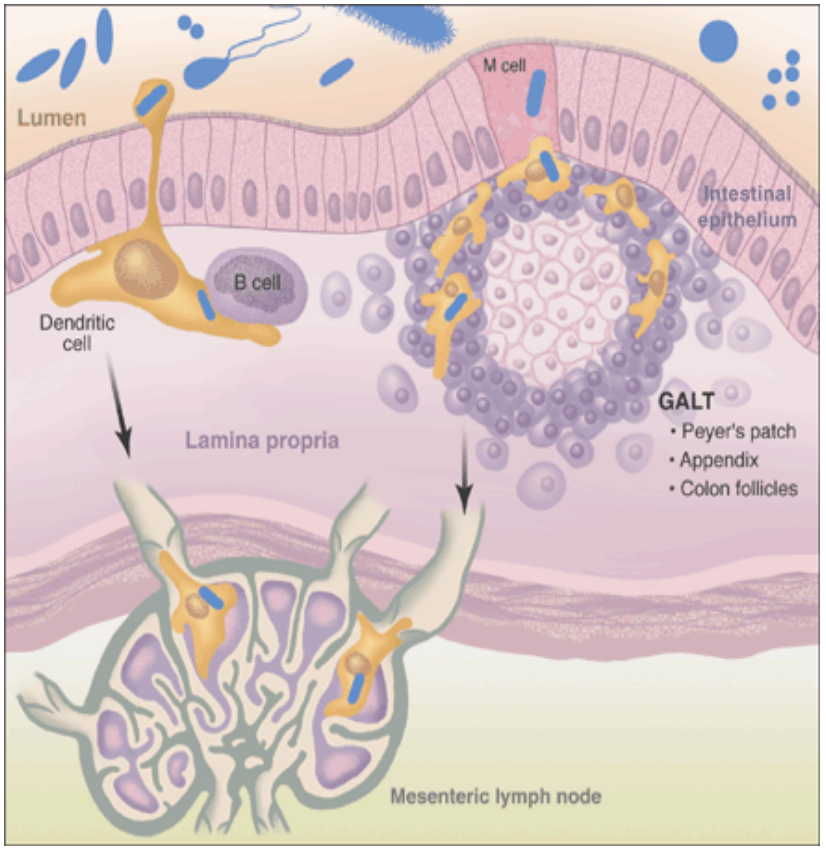


A specific case of dietary immunogens and their impact on Intestinal Integrity

β-mannans (β-galactomannans) molecule as an example

Intestinal Translocation, Intestinal hyperpermeability or Leaky Gut[28]

- **Intestinal Translocation** in principle is caused by any substance reaching the gut lumen by the oral route is eligible for translocation. This ranges from intact (macro) molecules to particles the size of tens of µ-meters. These particles may be live or dead including inert particles like starch, carbon, latex etc.



- **What Causes Translocation?**
- 1. Localized factor: Gut Microflora sampling: translocated micro-organisms are eliminated in a non-inflammatory way
- 2. Systemic factors affecting barrier function: toxins, malnutrition, parasites, infection, burns/shock, antibiotics.
- **Translocation** is a Routine immune defense function.

Increased epithelial permeability may be important in the development of chronic gut T cell–mediated inflammation[8,25]

Intact barrier

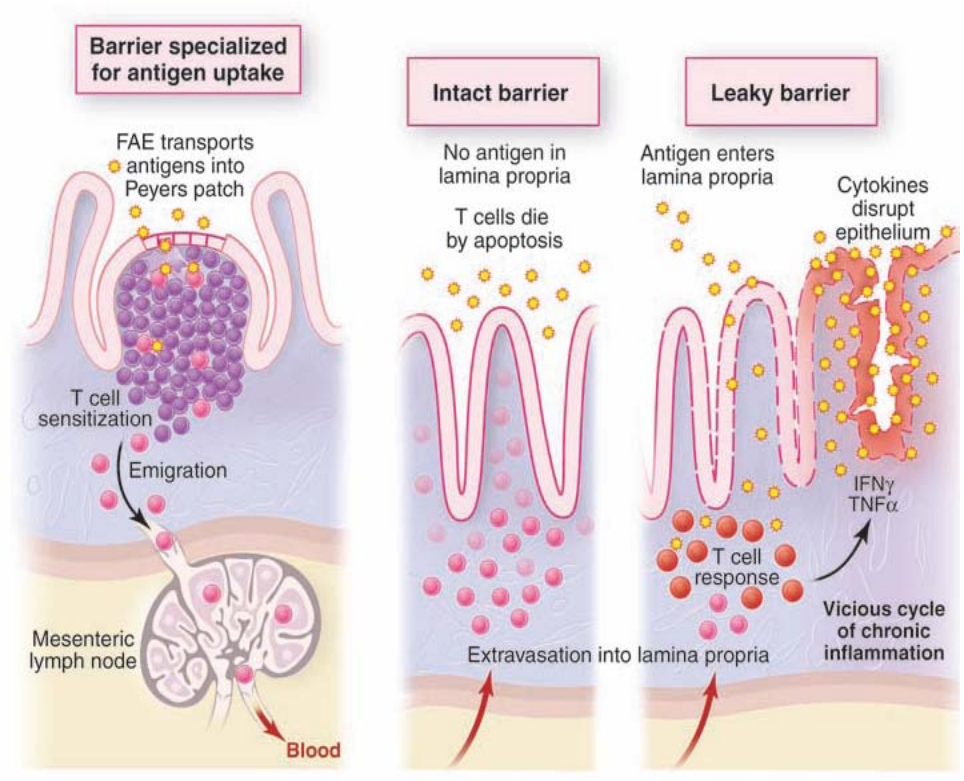
Dendritic cell and M-cell sampling luminal antigens (β-galactomannans) to effectively activate immune system[5.6].

Luminal antigens are not detected in lamina propria. (Local physiological inflammation)

Leaky barrier

Luminal antigens (β-galactomannans) rush into lamina propria and activate both local and systemic inflammation.

This may causes more tissue damage and creates chronic inflammation.

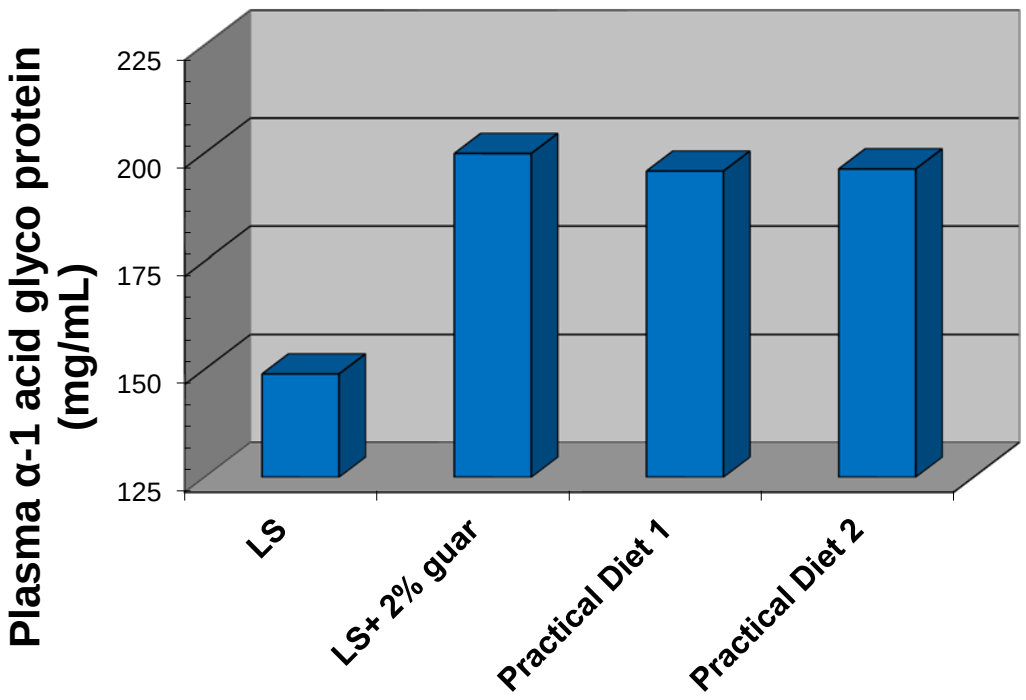


Evidences of translocation of β-galactomannans

β-galactomannans[13]

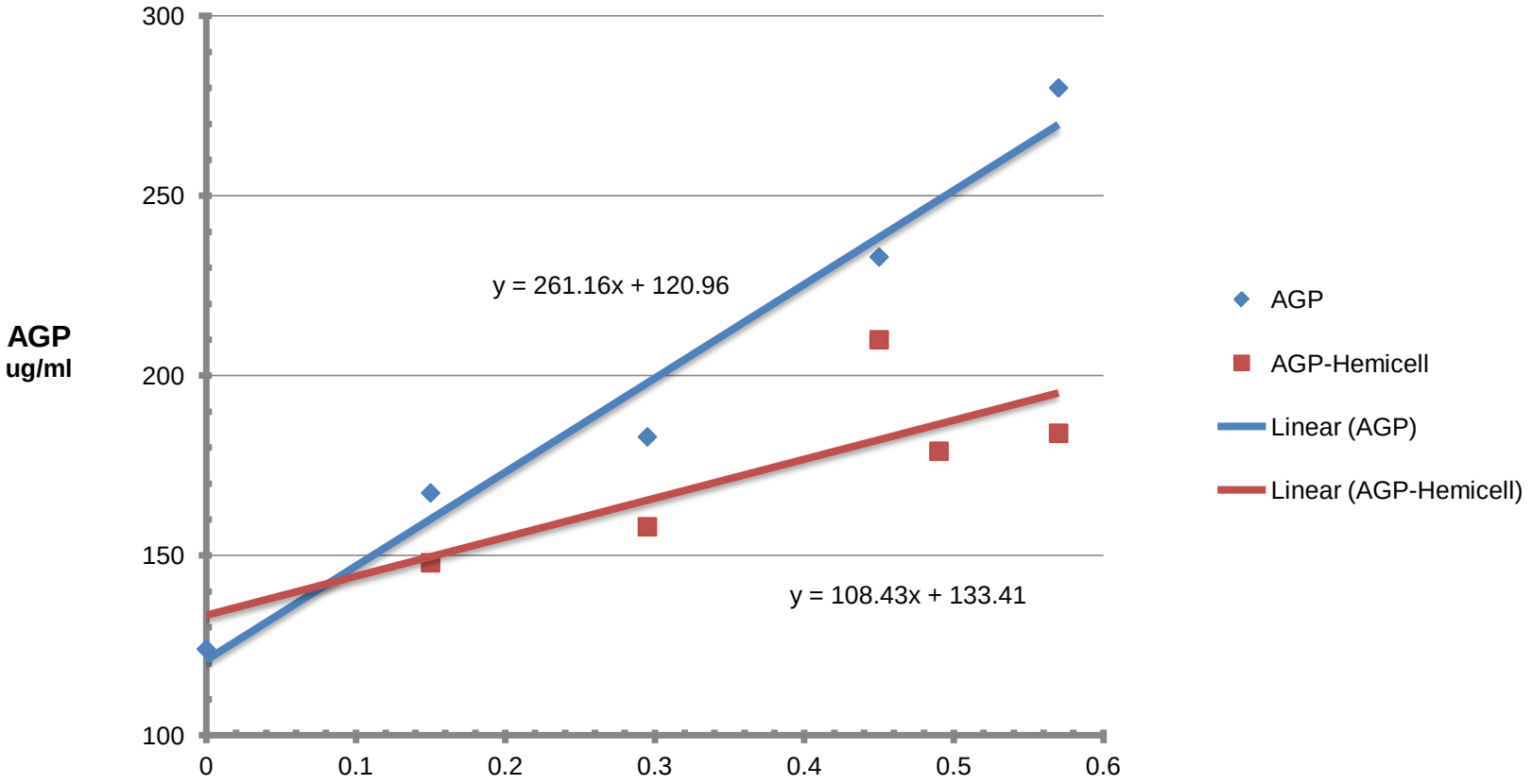
- β-galactomannans in the diet stimulate innate immune system

Low stimulation diet vs. practical diet*



* Diets designed by Nick Dale, University of Georgia

Linear correlation between circulating α-1-AGP and feed mannose content[26]



26. Anderson and Hsiao, 2009,

Effect of dietary fiber on the Immune function of Sprague-Dawley rats[27]

	Cellulose	PHGM*	Intact β-galactomannan)
MW, Da		20,000	220,000
Spleen			
IgA (ug/ml)	23.8±2.4^{ab}	24.4±2.5^{ab}	28.1±1.9^{a}
IgG (ug/ml)	123±10	124±5	111±8
IgM (ug/ml)	51.4±2.2^{ac}	52.6±1.6^{a}	44.7±2.3^{b}
Mesenteric Lymph Node			
IgA (ug/ml)	13.3±2.2^{a}	12.7±1.3^{a}	**25.5±2.6^{b}**
IgG (ug/ml)	36±6^{a}	34±2^{a}	**98±16^{b}**
IgM (ug/ml)	4.9±1.6^{a}	4.9±1.6^{a}	**13.3±3.5^{b}**

*Partially Hydrolyzed Galactomannans

•Yamada, Koji , et. al. *Bioscience Biotechnology and Biochemistry* 67 (2), 429- 433, 2003

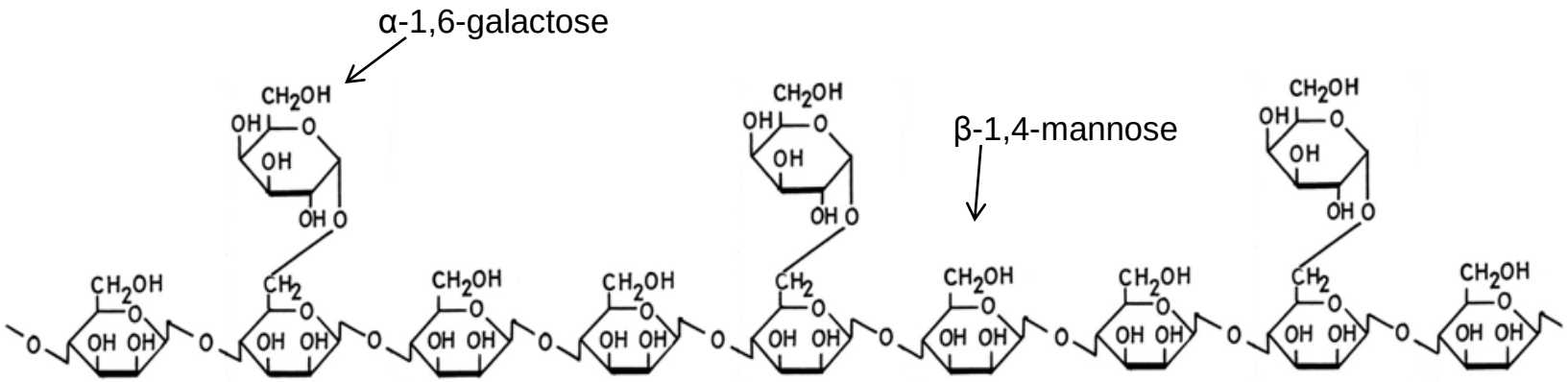
Elanco

Galactomannan intervention: Novel Strategy

Chemical structure of β-galactomannans[1,2,3]

- Beta-mannans are long-chain polysaccharides with a backbone of mannose and side chains of galactose and/or glucose

Legume galactomannan



β-galactomannans

- Commonly found in many legume & non-legume feed ingredients

β-galactomannan content* [1-4]

Ingredient	% β-galactomannan content, dry basis
Soybean hulls	6.0 to 10.0
Soybean meal 44%	1.5 to 1.8
Full fat soybeans**	1.2 to 1.5
Soybean meal 48%	1.0 to 1.5
Sunflower meal (34% CP)	1.0 to 1.2
Rapeseed expeller (10% fat)	0.83
Rye	0.70
Rapeseed meal (canola meal)	0.57
Barley	0.49
Peas	0.39
Oats	0.30
Wheat	0.10
Sorghum	0.09
Corn	0.09

*Estimate based on mannose content
** Calculated from SBM 44%

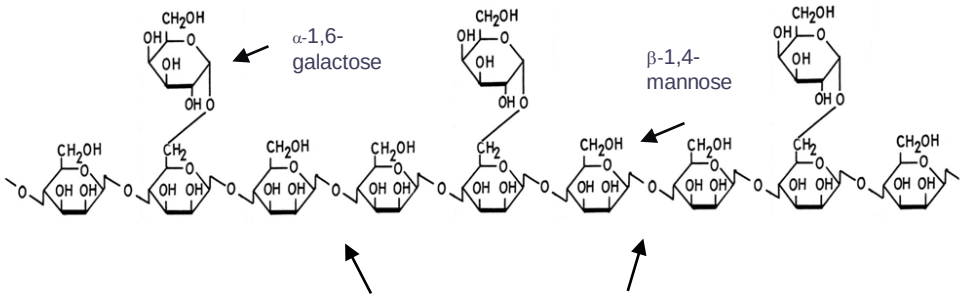
1. Hsiao, H., Anderson, D. and Dale, N. 2006. "Levels of β-mannan in Soybean Meal." Poultry Sci. 85(8): 1430-1432.
2. Slominski, B. and Campbell, L. 1990. "Non-starch polysaccharides of canola meal: quantification, digestibility in poultry and potential benefit of dietary enzyme supplementation. J. Sci. Food Agri. 53: 175-184.
3. Whistler, R. and Saarnio, J. 1957. "Galactomannan from soybean hulls." J. Am. Chem. Soc. 79: 6055-6057.
4. Dierick, N. 1989. "Biotechnology aids to improve feed and feed digestion: enzyme and fermentation." Archives of Animal Nutrition (Berlin). 3: 241-246

Elanco

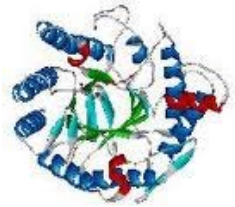
Intervene by degrading β-galactomannans in feed

- By fragmenting GM into oligosaccharides, it renders the oligosaccharides un-recognizable by immune cells and helps prevent Feed-Induced Immune Response (FIIR)[5,6]

Legume galactomannan

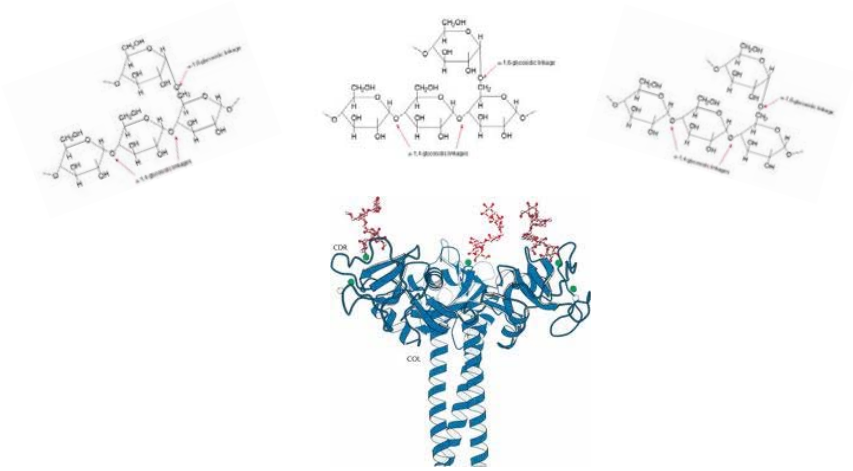


Hydrolysis Sites



Hydrolyzed molecule

(Mannose oligosaccharide)



Circulating Mannose Binding Lectin[29]

5. . Stahl, P.D. and Ezekowitz, R.A. 1998. "The mannose receptor is a pattern recognition receptor involved in host defense." Curr Opin Immunol. Feb; 10(1):50-5.
6. Beutler, B., Jiang, Z., Georgel, P. et al. 2006. "Genetic Analysis of Host Resistance: Toll-Like Receptor Signaling and Immunity at Large." Annu. Rev. Immunol. 24: 353-389.

Elanco

Research of intervention



Intervention= Energy Sparing Effect[18]



33 broiler peer reviewed articles 2002-2013[19]

$DWG_{Control}$ = 10,5 +143.91*DEI

$DWG_{\beta\text{-mannanase}}$ = 10,5 +147.84*DEI

1 kg

187 kcal

2,7%

Intake estimate of 1 Mcal (1000 kcal) of ME accounted for 143.91 g of weight gain in the control animals (DWG= 10.54 + 143.91x ; R2 = 0.95; where ' DWG ' is daily weight gain in grams , and 'X' is the intake of energy, expressed in Mcal). 147.84 g is the weight gain in animals receiving diets supplemented with β- mannanase (DWG+ = 10.45 + 147.84 x; R2 = 0.95). This relationship represents a saving of 2.7 % in energy expenditure for growth. From these equations, we were able to estimate that supplementation of diets with β- mannanase enables a saving of **187 kcal per 1 kg of live weight gain in broilers**.

Elanco

Conclusions

- Access to food is the main challenge for the next 40 years and broiler meat will continue to provide a major and increasing supply of the world's increasing animal protein requirements.
- Post-prandial inflammation is a major factor in growth in broilers (Korver et al., 1998, Niewold, 2007) and β - galactomannans are an example of typical feed aggressors, which stimulate the costly intestinal innate immune system and subsequently the adaptive immune system

Conclusions

- Effective intervention is one way of improving broiler performance by reducing unnecessary and wasteful inflammatory and innate immune responses to feed borne immunogens from commonly used feedstuffs such as soybean meal, sunflower and rapeseed. Hence, to maximize production, the immune system must be vigilantly maintained and activated only when necessary

- Research has shown that effective intervention leads to improved productivity and uniformity.

References

1. Hsiao, H-Y., Anderson, D. and Dale, N. 2006. “Levels of β-mannan in Soybean Meal.” Poultry Sci. 85: 1430-1432.

2. Slominski, B. and Campbell, L. 1990. “Non-starch Polysaccharides of Canola Meal: Quantification, Digestibility in Poultry and Potential Benefit of Dietary Enzyme Supplementation.” J. Sci. Food Agri. 53: 175-184.

3. Whistler, R. and Saarnio, J. 1957. “Galactomannan From Soy Bean Hulls.” J. Am. Chem. Soc. 79: 6055-6057.

4. Dierick, N. 1989. “Biotechnology aids to improve feed and feed digestion: Enzymes and fermentation.” Archives of Animal Nutrition (Berlin). 39(3):241-261.

5. Stahl, P.D. and Ezekowitz, R.A. 1998. “The mannose receptor is a pattern recognition receptor involved in host defense.” Curr Opin Immunol. Feb; 10(1):50-5.

6. Beutler, B., Jiang, Z., Georgel, P. et al. 2006. “Genetic Analysis of Host Resistance: Toll-Like Receptor Signaling and Immunity at Large.” Annu. Rev. Immunol. 24: 353-389.

7. Didierlaurent, A., Simonet, M. and Sirard, J-C. 2005. “Innate and acquired plasticity of the intestinal immune system.” Cellular and Molecular Life Sciences. 62: 1285-1287.

8. Spurlock, M. 1997. “Regulation of metabolism and growth during immune challenge: an overview of cytokine function.” J. Anim. Sci. 75: 1773-1783.

9. Gabler, N. and Spurlock, M. 2008. “Integrating the immune system with the regulation of growth and efficiency.” J. Anim. Sci. 86: E64-E74.

10. Korver, D. 2006. “Overview of the Immune Dynamics of the Digestive System.” J. Appl. Poultry Res. 15: 123-135.

11. Klasing, K. 2007. “Nutrition and the immune system.” Br. Poult. Sci. 48(5): 525-537.

12. Lee, J., Bailey, C. and Cartwright, A. 2003. “β-mannanase Ameliorates Viscosity-Associated Depression of Growth in Broiler Chickens Fed Guar Germ and Hull Fractions.” Poultry Sci. 82: 1925-1931.

13. Anderson, D., Mathis, G., Jackson, M. and Hsiao, H-Y. 2006. “Effect of β-mannanase (Hemicell® Feed Enzyme) on Acute Phase Protein Levels in Chickens and Turkeys.” Poultry Science Meeting, Edmonton, Alberta, Canada.

References

14. Korver et al., 1998 "Effect of dietary energy level and oil source on broiler performance and response to an inflammatory challenge" Poult. Sci. Vol. 77: 1217-1227.

15. Niewold, 2007 The Nonantobiotic Anti-inflammatory Effect of Antimicrobial Growth Promoters, the Real Mode of Action? A hypothesis¨. Poult. Sci. Vol. 86: 605-609.

16. Goldszmid, R.S. and Trinchieri, G.. 2012, "The price of immunity" Natural Immunology, Vol 13.

17. North American Field trial experience example.

18. Andretta, I, Kipper, M, Rodrigues de Quadros, V, Jackson, M. and Martinez Cummer, M.A. Meta-analysis study of interactions between productive performance and nutritional supplementation with Hemicell® in diets for broiler chickens. XIV European Poultry Conference, Stvanger, Norway 2014. Abstract 1153.

19. Fuglie, K., MacDonald, J., Ball, E. September 2007. "Productivity Growth in U.S. Agriculture." United States Department of Agriculture Economic Research Service. Economic Brief No. 9.

20. Havenstein, G., Ferket, P. and Qureshi, M. 2003. "Carcass Composition and Yield of 1957 Versus 2001 Broilers When Fed Representative 1957 And 2001 Broiler Diets." Poultry Sci. 82: 1509-1518.

21. Simmons, J. Technology´s Role in the 21st Century: Food Economics and Consumer Choice. Elanco Animal Health Newsletter March 2009.

22. Alexandratos, N. and Bruinsma J. World Agriculture Towards 2030/2050**.** The 2012 Revision ESA Working Paper No. 12-03 June 2012 Agricultural Development Economics Division Food and Agriculture Organization of the United Nations.

23. Banerjee, C. Market Analysis for Terrestrial Application of Advanced Bio-Regenerative Modules: Prospects for Vertical Farming. MSc. Disseration, Hohen Landwirtschaftlichen Fakultät der Rheinische Friederichs-Wilhelms-Universität zu Bonn July, 2012.

24 Swick, R.A., Wu, S.B. , Zuo, J. , Rodgers · Reza Barekatain, N.M. and Choct, M. 2013 Implications and development of a net energy system for broilers. *Animal Production Science* 53(11) 1231-1237

References

26. Thomas T. MacDonald and Giovanni Monteleone, 2005, "Immunity, Inflammation, and Allergy in the Gut", Science, vol.307 p 1920-1925.

25. Anderson, D. and Hsiao, H.Y. 2009. New Feed Enzyme Development. Chemgen Corp. pp. 1.30.

27. Yamada, K. , Tokunaga , Y., Ikeda, A. Ohkura, K.I., Kaku-Ohkura, S., Mamiya, S., Lim, B.O., Tachinama, , H. Effect of dietary fiber on the lmmune function of Sprague-Dawley rats*Bioscience Biotechnology and Biochemistry* 67 (2), 429- 433, 2003

28. Kraehenbuhl J.P., and Corbett, M. 2004 Gut Immune monitoring system: Keeping the gut microflora at bay. Vol. 303, Science

29. Weis, W.I. and Rickamer, K. 1994. Trimeric structure of a C-type mannose-binding protein. Structure Vol. 2:1227-1240