final report

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Prepared by: Kirthi De Silva

CSIRO Food and Nutritional Sciences

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Meat & Livestock Australia Limited
Locked Bag 991
NORTH SYDNEY NSW 2059

MLA Bioactives Workshop

October 2011

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Executive summary

The 2011 MLA bioactives workshop was held from 11th to 13th October. Day 1 was held at the CSIRO Food and Nutritional Sciences, Werribee site, with day 2 and 3 held at the Crowne Plaza Hotel, Melbourne. The workshop included a site visit to Murray Goulburn co-operative Company, Leongatha and CSL Limited, human plasma processing facility in Broadmeadows, Victoria.

On the first day of the workshop, 3 presentations on the business case for bioactives, potential uses of blood proteins and the technologies used to extract and separate bioactives were made. This was followed by pilot scale demonstrations of extraction and separation technologies used in the food industry. The pilot scale demonstrations included the use of enzyme technology to hydrolyse and extract bioactives from cellular material, e.g. bovine trachea and a demonstration of separating two minor protein components of milk using continuous separation (CSEP) technology, a form of simulated moving bed chromatography.

The attendees made site visits to Murray Goulburn Cooperative Co, Ltd where CSEP technology is used at commercial scale to separate minor proteins from milk, and to CSL where human blood plasma is fractionated into different fractions using chromatography and membrane filtration technology.

1 Background and project objectives

1.1 Background

Opportunities exist to significantly increase the value of carcases in both beef and sheep processing by the production of high value pharmaceutical and food ingredients from meat processing co-product streams. MLA has identified five bioactive products which, if manufactured in Australia, could provide a net benefit to the industry of ~$30m pa.

MLA has over the past 5 years conducted a series of workshops on bioactives to facilitate the capture of the opportunities to value add to meat processing co-product streams. The workshops conducted to date have focussed on market opportunities, project selection strategies and the estimation of capital and production costs. The current workshop focused on providing a practical and interactive demonstration of the pilot scale technology used to produce bioactives at commercial scale.

1.2 Project objectives

The objectives of the workshop included:

- To present and demonstrate to Australian meat industry representatives, at pilot scale, opportunities to achieve significant impact on the sustainability of the red meat industry through value addition to co-product streams by extracting, separating and recovering valuable bioactive ingredients. The demonstrations to include digestion of solid co-products to extract bioactives and separation of molecules from liquid streams utilising technologies such as membrane filtration and chromatography.
- To facilitate discussions with industry participants on commercialisation opportunities and challenges in value-adding to co-product streams through bioactive separations.
- To conduct a tour of CSIRO's pilot plant and organise industry visits to demonstrate and understand the scale and reality of large scale processing as applied in the dairy and pharmaceutical industries.
- To undertake site tours to dairy and pharmaceutical facilities currently producing bioactives at commercial scale.
- To provide opportunities for interaction between industry participants, researchers and suppliers.

2 Workshop – day 1

Presentations were made before the tour of the CSIRO food processing facilities, including a demonstration of separation technologies for bioactives. There were 18 industry participants and researchers at the workshop on day 1.

Figure 1. MLA workshop participants at the CSIRO food processing facility demonstration of extraction and separation technologies for bioactives. The continuous separation (CSEP) pilot plant is in the background.

2.1 Business case for bioactives – Duncan Veal, Commercialisation Manager, MLA

Data were presented on the global biotechnology supplies market and the breakdown of the expenses along the value chain to manufacture and market biotechnology products. The dairy industry, particularly Murray Goulburn (MG), was taken as an example of extracting value from co-product streams. The discussion on the examples of extracting value in the dairy industry ranged from low value, low cost commodity ingredients to high value, high cost nutraceutical and pharmaceutical products. A comparison of extracting value from blood similar to dairy streams was discussed.

The development of new processes to stabilise plasma leading to new application of plasma proteins in food, nutraceuticals and pet food was identified as the reason for increased demand for plasma. The market for blood based bioactives, especially bovine serum albumin (BSA) was also discussed in detail. Regulatory hurdles in different countries, understanding marketing dynamics and the development of recombination products were highlighted as potential hurdles in developing a red meat based bioactives industry.

The conclusions reached in the presentations were that high value animal products offer significant opportunity for the red meat industry, and to capture these opportunities, partnering early in the development stage was essential for success. Partnering is essential to overcome marketing risks, understanding customer needs, legal and business needs and to understand scientific and technical needs. In addition, developing a business plan was highlighted as critical for success.

2.2 Blood proteins potential use – Lyndon Kurth, Theme Leader, CSIRO

Information was presented on the global food industry drivers and the megashocks that the world faces over the next 50 years. These include food security with the need to increase food production due to increase in population and the increase in health care costs related to diet and lifestyle related risk factors. The challenge faced by the food industry is to double global food production with half the water, land use and energy amid climate change.

Information was also presented on plasma and its functionality. The functionality of plasma investigated by most researchers includes solubility, emulsifying, foaming and gelling properties. It was noted that no standard methods were used in the scientific literature to assess the functional proprieties of plasma and other protein therefore, the comparison of the functional properties of different proteins with plasma proteins was difficult. Research on plasma protein functionality has demonstrated good solubility, emulsifying, foaming and gelling properties.

The recommendations reached in the presentation were that the meat industry should evaluate the economics of recovering blood proteins to a food-grade standard and consider the cost/benefit of producing plasma derived food ingredients. The creation of functional ingredients will require product and process development based on sound scientific understanding of the proteins.

2.3 Bioactive extraction and separation – common unit operations – Kirthi De Silva, Team Leader, CSIRO

Information was presented on different process scale separations used in the food industry. The quality of the protein products and the safety issues in using chemical solvents or a combination of solvents and heat precipitation was discussed. Details on gentler processing technologies such as chromatography and membrane filtration were also presented. This included the different forms of chromatography used in the food industry and the different types of hardware available for process scale chromatography. The features, advantages and disadvantages of different chromatographic systems were also discussed.

The principles of membrane filtration were presented together with membranes of different pore sizes and made of different materials. The advantages and disadvantages of each of the different membrane systems together with applications of membrane in food processing were discussed.

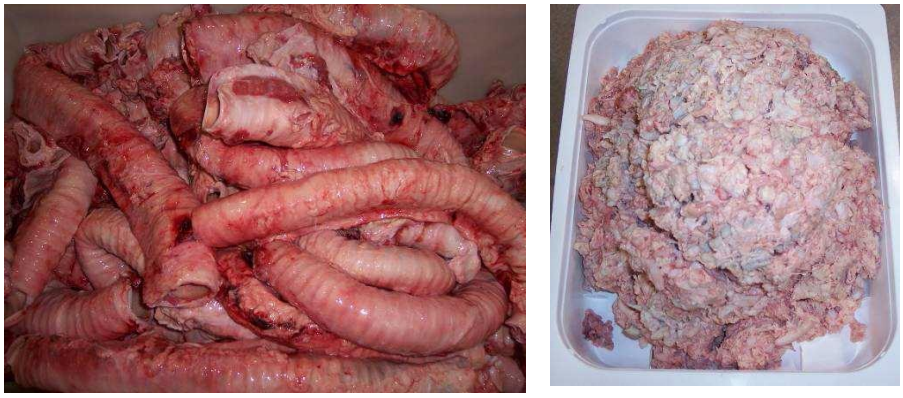
The use of enzymes to produce bioactive peptides by the proteolytic cleavage of proteins was discussed. Examples of the use of enzymes to extract bioactives from cellular matrices such as the extraction of chondroitin sulphate from cartilage were also discussed.

2.4 Demonstration of extraction and separation technologies – Kirthi De Silva and Filip Janakievski, CSIRO

Two pilot scale technologies that are amenable to scale-up to commercial production were demonstrated. The participants were able to observe the technologies in operation and ask questions. The demonstrated technologies were:

- Conversion of minced trachea to a liquid form to enable extraction of chondroitin sulphate using proteolytic enzyme reactions.

- Use of simulated moving bed chromatography using CSEP technology to separate and fractionate two minor protein components of milk, lactoferrin a red coloured protein and lactoperoxidase fraction, a brown coloured protein fraction. On the site visit to Murray Goulburn (MG) on day 2, the participants were able to observe the commercial application of CSEP technology in the dairy industry.



(A) (B)

Figure 2 Bovine trachea (donated by Wagstaff Cranbourne Pty Ltd) as supplied (A) and after mincing and used as the feed material for the proteolytic hydrolysis demonstration (B).

Figure 3. Jacketed mixing vessel used for proteolytic hydrolysis of minced trachea.

3 Site Visits

3.1 Murray Goulburn Cooperative Co., Leongatha – day 2

Murray Goulburn (MG), Leongatha milk processing facility is approximately 140km from Melbourne. The facility processes milk to produce long life milk and caseinates. The company also produces lactoferrin, a bioactive ingredient at the facility. The production of lactoferrin is achieved using CSEP technology which is a form of simulated moving bed chromatography.

The details of the lactoferrin process were provided by Ken Thomas. On return from the MG facility, there was a discussion among the participants based on their observations and information provided by Ken Thomas. The comments made by the participants were recorded and are below:

- Conventional milk products: $2,000-3,000/tonne
- Lactoferrin (LF) medical grade as produced at Leongatha: $800,000/tonne
- TGA (Therapeutic Goods Administration, Australian) accreditation process is underway
- US FDA (USA Food and Drug Administration) accreditation of medical LF is also underway
- Operation of CSEP is "difficult" because there are a lot of settings to get right, but that some flexibility makes CSEP adaptable to either new products or new grades of existing products, e.g., used to increase purity from 95% up to 99.9%, which results in an approximate doubling in price in the market place.
- The Leongatha process operates on a 72hr cycle: 12hr cleaning / sterilising and a 60 hr run i.e. process runs 24hrs a day for 2½ days before a thorough cleaning cycle takes place.
- Value adding is a continuing process - new fractions with new bioactives are being developed all the time.
- The one plant gives multiple products by tweaking eluents (the liquid solutions used to desorb the products from the resin in chromatography)
- LF selection: was emerging interest at the time, seemed like a fit. CSIRO (FSA) gave a competitive advantage.
- In hindsight, MG would have partnered with market pull company
- A recombinant LF product is available but is not considered a threat
- Research now on clinical applications in the “sports recovery” area rather than in the mainstream food area.
- Future products will be in the areas of: bone health; gut health; metabolic disease; sarcopenia (muscle wastage)
- MG see their competitive advantage in the source and purity of their LF, its medical efficacy plus TGA and US, FDA accreditation
- MG sell crude LF plus IGG to a Japanese customer
- MG experience with regard to risk management: When taking on a new market/product they emphasized the importance of partnering with value adder/pharmaceutical company to assist in the path through regulation and distribution to the customer
- MG had a vision for the future and took a chance. They are now planning on further products/expansion of the the business. i.e., MG Nutritionals is a business dealing with dairy derived bioactives, not a lactoferrin business.
- CSEP has been versatile – expandable
- The original vision to generate a series of value added protein products was generated at board of directors level (Wayne Sanderson). This sort of management commitment to the business was essential in providing the time and resources to build the MG Nutritionals business.

- Patient money and a long payback period were acceptable to the company.
- An active operational company champion (Ken Thomas) was also key – KT saw selection of dedicated and committed process development staff as being essential.
- The original vision for the Leongatha plant was to build it to pharmaceutical standard, but the first plant at Cobram was for less ambitious food grade nutraceutical products.
- MG's business strategy was one of entering the bioactives market with a relatively crude product and moving to more refined products.
- Total Leongatha investment for a million litre/day pharmaceutical plant was:
    - Capex $15m
    - R&D over 13 years, $10m (for current and next wave of products)
    - Regulatory (to medicinal LF product) $5m
- When the first CSEP plant was commissioned, it took ~3 years to fine tune and optimize.
- During this optimization, the product purity improved from 50% to 80%.
- Value added product was seen as a way of avoiding commodity price oscillations.
- Lactoferrin allowed entry into the nutritionals space. "MG Nutritionals" was established to manage the business because it was realised that a value added product business model is different to the cost focused commodity model.
- MG recognised that they also had to capture co–products and find markets for them in order to establish a stable business. The issue is that after the bioactives are removed from the milk it can no longer be sold as milk even though less than .01% is removed in producing lactoferrin – gave example of the EU companies which failed. MG sells other fractions such as casein – again a good example of the need to commit to a business rather than to a product.
- Looking forward, MG will produce more than lactoferrin, and has used the R&D investment to develop a pipeline of "follow on" products.
- Regulatory requirements were recognised at the outset and were incorporated into the design of the very first plant.
- The first venture into bioactives was a food product at the Cobram plant. Once in the business, they developed value chain customers and were able to further diversify.
- IP: Has value but one should expect that people can get around it.
- Being first to market was seen to be a benefit.
- LF product choice in the first plant (Cobram) was a good choice because the proteins selected were "robust" and relatively easy to handle during purification
- Used industry knowledge and science networks to identify targets.
- Keeping the champion is critical – career path? Rewards? Depth of expertise? Succession planning?
- Value added products required a different business model.
- Separation can concentrate not only the target compound but also contaminants – caution is required.
- Treat the process from a holistic perspective, considering purity of main product, contaminants, downstream coproducts etc.
- Feedstock for high value products may need to be handled differently to that for commodity product
- Bold step to build a plant capable of supplying 100% of world market as estimated at time of investment.

3.2 CSL Ltd, Broadmeadows – day 3

The CSL plasma processing facility is located in Broadmeadows approximately 15km from the Melbourne CBD. The facility processes plasma from blood donated by volunteers through the Red Cross blood collection system. The plasma is fractionated using multiple separation technologies to produce different plasma fractions. The production process is conducted in specially built good manufacturing practice (GMP) facilities. The participants were taken on a tour of the plasma processing facility by Dr Joseph Bertolini, R&D Manager.

On return from the CSL facility, there was a discussion among the participants based on their observations and information provided by Joseph Bertolini. The comments made by the participants were recorded and are below:

- CSL has similar equipment to MG but better quality finish on stainless equipment.
- At CSL, raw materials are processed in batches whereas at MG raw material was processed in a continuous fashion. Whereas MG used a CSEP unit for the chromatographic step, CSL use a number of batch columns ~1.6m diameter 30cm deep.
- CSL is a mature business which evolved and then expanded after the company was floated.
- CSL had a higher proportion of QC and R&D staff to process operators than was the case in MG.
- CSL raw material is blood plasma collected from donations in a number of different countries. It is therefore “free”, but the costs of regulatory compliance and QA and records is high because the final product has to be absolutely pure as it is injected directly into the patients’ veins.
- CSL leveraged their know-how and production capacity by toll manufacturing i.e. contract production for other countries.
- CSL may have exhausted the products from plasma and are beginning to diversify into recombinant products and chemically modified products (modified for improved effectiveness as medicines). MG’s diversification by comparison is into other extractable products. The key observation is that both companies are working on their next generation of products at the same time as they are building sales and finessing production of current products.
- Products don’t need to be limited by current feed-stocks.
- Research activity needs to be part of the business development strategy
- Each bag of plasma (i.e. each individual donation) is characterised for antibodies against a number of common antigens such as tetanus toxin. Those with higher levels of certain antibodies are grouped together and processed in batches of 400L. There may be opportunities to do something similar in the red meat industry – creating a range of products from the natural variation in raw materials.

4 Appendices

4.1 Appendix 1 – Bioactives Workshop Program Invitation

'We can *do* this!'

Two and half day workshop

11th -13th October 2011 – Melbourne

Meat & Livestock Australia is pleased to announce the latest in its series of bioactives workshops.

Previous workshops have focused on market opportunities, project selection strategies and tools for production cost estimation.

This workshop will be a **practical** and **interactive** demonstration of how bioactive products can be produced successfully at a commercial scale. **Site visits** to companies producing bioactives and laboratory sessions will complement presentations and group activities to demystify the bioactives value adding opportunities and key technologies.

Attendance at the workshop, site visits and dinner on Wednesday 12th October is *free*. Participants are responsible for their own accommodation and travel costs.

Tuesday 11th October*
CSIRO Food and Nutritional Sciences
671 Sneydes Road, Werribee, Victoria

Site visits
Murray Goulburn, Leongatha
CSL, Parkville

Wednesday 12th & Thursday 13th October*
Crowne Plaza Melbourne

*Accommodation is available at the Crowne Plaza Melbourne. Transport from CSIRO to the hotel on Tuesday 11th October will be provided.

Workshop presentations and highlights

- Demonstration of extraction, separation and recovery techniques to extract bioactive ingredients from co-product waste streams in a pilot plant
- Practical laboratory sessions

- Commercialisation opportunities and challenges in value-adding to co-product streams through bioactive separations
- Site tours at dairy and pharmaceutical facilities currently operating at large scale
- The bioactives value chain and developing relationships
- Developments in the MLA bioactives program
- Project development opportunities
- Secure feedback to ensure alignment of the MLA bioactives program with industry needs.
- Opportunity to interact with industry researchers and suppliers

Networking dinner

Meat & Livestock Australia are pleased to offer an invitation to all participants to attend dinner on **Wednesday 12th October**. This dinner is free to all workshop participants.

The dinner will be held at

SQUIRES LOFT
818 Bourke Street
Docklands VIC 3008

6.30pm for 7pm seating

The venue is a short walk from the Crowne Plaza.

Workshop participants are also welcome to attend dinner at the hotel on Tuesday 11th October. This dinner will be at the participants' own cost.

Program – day one

Tuesday 11th October 2011 - *CSIRO Food & Nutritional Sciences*

Unit operations demonstration

Time	Session	Speaker
11.30 – 12.00	Registration and lunch	
12.00 – 12.20	Welcome	Lyndon Kurth, CSIRO
12.20 – 12.45	Introduction and plan for the workshop	Phil Franks, MLA
12.45 – 1.20	Business case for bioactives – Pharmaceutical applications	Duncan Veal, MLA
1.20 – 2.00	Blood proteins potential use - food ingredient applications	Lyndon Kurth, CSIRO
2:00 – 2.30	Typical bioactive extraction and purification processes, common unit operations	Kirthi De Silva, CSIRO
2.30 – 4.10	Practical demonstrations of : 1. hydrolysis reactions to extract bioactives from tissues and organs 2. chromatography - separating bioactives from liquid streams 3. membranes to purify and concentrate bioactives in liquid streams	CSIRO Food Processing Centre
4.30 – 5.45	Scaling up – How does it work?	Expert panel and discussion
5.45	Close - Return to City	

Program – day two

Wednesday 12th October 2011 *Crowne Plaza Melbourne*

Large scale extraction & separation

Time	Session	Speaker
08:15	Bus Departs from Crowne Plaza to Leongatha	
10.30 – 12.30	Site visit – Murray Goulburn, dairy bioactive separation process	MG representative
12.30 – 1.30	Lunch	
1.30 – 3.30	Bus to Crowne Plaza	
3.30 – 4.30	Pilot plant to commercial production – putting it in perspective	CSIRO Milton Hearn MLA
4.30	Afternoon tea	
4.30 – 5.00	Emerging separation and purification technologies	Milton Hearn, Monash University
5.00 – 5.30	CFNS presentation on - separations and value addition - technology transfer - commercialisation issues	Lyndon Kurth
5.30 – 6.00	Equipment and technology options	

Program –day three

Thursday 13th October 2011
08:15 – 16:00

Bioactives extraction & separation – Pharma applications

Time	Session	Speaker
8:15	Bus Departs from Crowne Plaza to CSL	
9.45 – 11.30	Site visit - CSL Parkville, Pharma separation process Presentation – Accreditation, process development, scale up and utilisation of meat derived bioactives in Pharma	CSL representative
11.30	Bus for Crowne Plaza	
12.30	Lunch	
1.00 – 2.30	Business models and managing risk	Michael Vitale
2.30 – 3.00	A value adder's perspective	TBA
3.00 – 3.30	A processor's perspective	TBA
3.30 – 4.00	Closing remarks	Philip Franks, MLA

The workshop program is subject to change.

4.2 Appendix 2 – Bioactives Workshop Attendees

2011 Bioactives Workshop Attendees List				
COMPANY	**FIRST NAME**	**SURNAME**	Position	Email
MLA	Philip	Franks		pfranks@mla.com.au
MLA	Duncan	Veal		dveal@mla.com.au
MLA	Joshua	Whelan		
CSIRO	Lyndon	Kurth		
CSIRO	Kirthi	De Silva		
Murray Goulburn	Ken	Thomas		
Monash University	Milton	Hearn		
CSL	Unknown	Unknown		
CSIRO	Simone	Osborne	Research Scientist	Simone.Osborne@csiro.au
GE Healthcare Life Sciences	Tanya	Lewanowitsch	BioProcess Product Specialist	tanya.lewanowitsch@ge.com
JBS Australia	Julian	McKie	Byproducts Marketing	jmckie@jbssa.com.au
Corelli Consulting	Dianne	Glenn	Principal	dianne.glenn@coreli-consulting.com
Monash university	Michael	Vitale	Professor	michael.vitale@monash.edu
Flinders University/Dep. Medical Biotechnology	Susanne	Zeile	Research Scientist	susanne.zeile@flinders.edu.au
Cool Off	Edward	Staughton	Managing Director	edward@cooloff.com.au
Flinders University	Julian	Adams	Research Fellow	julian.adams@flinders.edu.au
Wagstaff Cranbourne P/L	James	Ralph	Director	jhralph@bigpond.net.au
CSIRO	Katrina	Spencer	Business Development Manager	katrina.spencer@csiro.au

HW Greenham	Darren	Maloney	Operations Manager	dmaloney@greenham.com.au
Neumann Biotech	Simon	Tooth	CEO	simon@neumannbiotech.com
Neumann Biotech	Jat	Tran		
Neumann Biotech	Joe	Carra		
Neumann Biotech	Soumya	Sv		
CSIRO	Robyn	Warner		robyn.warner@csiro.au