Institution: University of East Anglia

Unit of Assessment: 3A - Allied Health Professions, Dentistry, Nursing and Pharmacy: Pharmacy

Title of case study:

The fisheye lens: a journey from human health to aquaculture

1. Summary of the impact

Sanderson's research focuses on cataract formation in humans. In the 1990s, cataracts became prevalent in EU farmed salmon causing reduced growth, increased disease susceptibility and annual losses of €27.9M in Norway alone. Working with the Norwegian National Institute of Nutrition and Seafood Research and industrial partners, Sanderson applied her expertise to the salmon lens to overcome this problem. The research showed that the amino acid histidine is essential to salmon lens physiology. Therefore, the dietary requirements of farmed salmon were reviewed worldwide and histidine was specifically added to fish feed. The incidence of cataract formation is now drastically reduced, with major economic benefits.

2. Underpinning research

Julie Sanderson (Senior Lecturer, 1997-present) is an expert in eye disease. During a Fellowship funded by the Royal National Institute of Blind People, she developed a model to investigate cataract formation and was the first to maintain human lenses in culture for extended periods [1]. Her knowledge and expertise led to participation in an EU-funded initiative (FAIR PL 97-3963; 1999-2000) to research a serious problem in aquaculture, namely the dramatic increase in cataract formation in farmed salmon in the 1990's, with up to 80% of the individuals being affected. This was shown to be due to the removal of blood meal from fish feed, a consequence of concerns with contamination from "mad cow disease". Sanderson adapted her human eye techniques to develop *in vitro* models of salmon lens pathophysiology and understand the underlying cause of cataract formation.

The initial success led to collaboration between UEA, the Norwegian National Institute of Nutrition and Seafood Research, the Norwegian School of Veterinary Medicine and industrial partners *Biomar Ltd* (Scotland) and *Marine Harvest* (Norway) into the mechanism of cataract outbreaks in farmed salmon. The UEA team, led by Sanderson together with **Jeremy Rhodes** (Senior Research Associate, School of Biological Sciences), carried out research on cataract formation with their eye models and participated in feeding trials in Norway to investigate the effect of dietary supplementation.

In their first publication, the results of a 26-week feeding trial with two strains of Atlantic salmon were reported, showing that levels of the amino acid histidine led to a significant decrease in cataract formation [2]. A study with radiolabelled histidine indicated that the amino acid is rapidly converted to *N*-acetyl histidine and that this metabolite has a high turnover in the salmon lens [3]. Further investigation identified *N*-acetyl histidine as vital to salmon lenticular volume regulation and crucial to maintaining osmoregulation [4]. This is absolutely essential in salmon as they undergo changes in their osmotic environment moving between sea and freshwater (farmed salmon are hatched and raised in freshwater tanks up to 12-18 months old before transfer to sea cages). If insufficient histidine is provided by the diet, lens volume regulation mechanisms are impaired, leading to lens clouding and, ultimately, blindness. A later publication compared the traditional marine-based salmon diet with plant-based feed and highlighted the positive effects of histidine naturally present in the former [5].

Key findings of these studies were:

- supplementation of the diet with histidine reduced cataract formation in salmon [2, 3]
- identification of an "at risk" period where the level of histidine is critical for ocular health [3]
- histidine supplementation increases levels of histidine and *N*-acetyl histidine in the lens [2, 3]

- levels of *N*-acetyl histidine increase during the smoltification process (the process of adaptation from fresh to sea water) [4]
- *N*-acetyl histidine is a novel osmolyte in the salmon lens [4]
- animal feed that naturally contains histidine or feed supplemented with the amino acid is superior to plant-based fish feed in reducing the risk of cataract formation [5]

3. References to the research

(UEA authors in bold)

Publications

1. **Sanderson J**, **Marcantonio JM**, and **Duncan G**. (2000) A human lens model of cortical cataract: Ca^{2+}-induced protein loss, vimentin cleavage and opacification. *Investigative Ophthalmology and Visual Sciences* **41**: 2255-2261
2. Breck O, Bjerkas E, Campbell P, **Rhodes JD**, **Sanderson J**, and Waagbo R. (2005) Histidine nutrition and genotype affect cataract development in Atlantic salmon, *Salmo salar* L. *Journal of Fish Diseases* **28**: 357-371 doi: 10.1111/j.1365-2761.2005.00640.x
3. Breck O, Bjerkas E, **Sanderson J**, Waagbo R, and Campbell P. (2005) Dietary histidine affects lens protein turnover and synthesis of *N*-acetylhistidine in Atlantic salmon (*Salmo salar* L.) undergoing parr-smolt transformation. *Aquaculture Nutrition* **11**: 321-332 doi: 10.1111/j.1365-2095.2005.00362.x
4. **Rhodes JD**, Breck O, Waagbo R, Bjerkas E, and **Sanderson J**. (2010) *N*-Acetylhistidine, a novel osmolyte in the lens of Atlantic salmon *(Salmo salar* L.). *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* **299**: R1075-1081 doi: 10.1152/ajpregu.00214.2010
5. Trosse C, **Rhodes JD**, **Sanderson J**, Breck O, and Waagbo R. (2010) Effect of plant-based feed ingredients on osmoregulation in the Atlantic salmon lens. *Comparative Biochemistry and Physiology B-Biochemistry & Molecular Biology* **155**: 354-362 doi: 10.1016/j.cbpb.2009.12.002

Research Funding

Importance of dietary histidine, iron and zinc concentrations on cataract development in two strains of Atlantic salmon: Research grant £50,000 **Sanderson J**.
Norwegian Research Council and Hydro Seafood (2000-2003)

General requirement and cataract preventative effect of dietary histidine relative to dietary lipid sources in Atlantic salmon: Research grant £9,000 **Sanderson J, Rhodes JD**
Norwegian Research Council (2006-2009)

4. Details of the impact

In the late 1990s, cataracts became widespread in farmed Atlantic salmon in Ireland, Norway and Scotland. This was correlated with the removal of blood meal from salmon feed due to the potential health risk of contamination by scrapie and related prion proteins. The economic impact of these outbreaks was modelled and indicated the severity of the problem:

> **"The annual direct costs of cataracts [to the Norwegian farmed salmon industry] was estimated to be €27.9 million"**

(Corroborative Source **A**).

To put this in perspective, this was costlier than the most important diseases of swine and poultry within the UK at the time (ca. €20.4 million) and was a major cause of concern for the EU fishing industry. Sanderson was approached to find a solution to this problem and her research fulfilled this objective. The work identified histidine and its metabolite *N*-acetyl histidine as essential for salmon lens physiology. In addition, it provided a mechanistic understanding by defining the role of

N-acetyl histidine in salmon lens osmoregulation and strongly suggested that histidine deficiency was responsible for the cataract outbreaks observed in farmed Atlantic salmon. These results were immediately applied in the field and confirmed by feeding trials with control groups compared to salmon fed with supplemented histidine (reference 2 above).

The results of the research were rapidly disseminated and led to changes in salmon feeding practice within the EU fishing industry with an immediate economic benefit. Due to the dietary intervention, cataract formation in EU farmed salmon has been virtually eradicated with an annual economic impact of millions of pounds. As stated by the Global Research Manager at *Marine Harvest*, the largest supplier of farmed salmon with worldwide fishery sites, and accounting for 20% of global production:

> **"The research demonstrated the causal role of a deficiency in dietary histidine in cataract formation. Cataract in farmed salmon presented a considerable problem to the aquaculture industry, resulting in severe financial losses. Since increasing dietary histidine levels, further outbreaks of severe cataract has rarely been observed, presenting a consequent saving to the salmon farming industry. This research has therefore had a significant global impact on a multi-billion dollar industry.''**

(Corroborative Source **B**).

A Senior Research Fellow at the Section for Epidemiology and Biostatistics, Norwegian School of Veterinary Science, who modelled the economic cost of cataract formation says

> **"As of today, cataract incidents in farmed salmon are rare and the disease does no longer present a significant economic impact on the salmon farming industry. The EU concerted action, and the UEA research group to which Dr Sanderson belonged, thus played a key role to identify the main causative factor and to remedy the cataract problem in Atlantic salmon farming."**

(Corroborative Source **C**).

Subsequently, Sanderson's research has had reach and significance beyond the EU community and created a global awareness of the importance of dietary histidine in farmed salmon. In their report on the nutrient requirements of fish and shrimp, the American National Research Council of the National Academies discusses the beneficial effects of histidine in reducing cataract formation in farmed salmon and cites Sanderson's references 2 and 3 above (Corroborative Source **D**). Similarly, the United Nations Food and Agriculture Organization (FAO) highlights cataract formation as a deficiency disease in salmon farming, citing Sanderson's reference 2 from above:

> **"In Atlantic salmon, cataracts develop in certain genetic strains during the smoltification and post-smoltification periods. Several dietary factors are implicated in the pathogenesis, including histidine deficiency…."**

(Corroborative Source **E**).

The Japanese company *Kyowa Hakko Bio*, a major producer of amino acids by fermentation or by chemical synthesis, asked for authorisation to include its commercial L-histidine monochloride as a supplement in salmon feed. This was considered by the European Food Safety Authority and the product was approved for use in aquaculture (Corroborative Source **F**).

Currently, producers of salmon feed have modified their formulations to incorporate sufficient histidine content, particularly during the "at risk" period identified by Sanderson (reference 3 above). For example, Skretting, the world's largest supplier of farmed fish feed, state for their salmon smolt feeds, "Formulated to meet a minimum level of histidine at critical times of year to help prevent cataract" (Corroborative Source **G**).

5. Sources to corroborate the impact

A. Menzies FD, Crockford T, Breck O, and Midtlyng PJ. (2002) Estimation of direct costs associated with cataracts in farmed Atlantic salmon (*Salmo salar*). *Bulletin of the European Association of Fish Pathologists* **22**: 27-32 http://eafp.squarespace.com/bulletin-archive/2002-volume-22/issue-1/

B. Corroborating letter from the Global Research Manager, *Marine Harvest*, Bergen, Norway
Copy held on file at UEA.

C. Corroborating letter from the Section for Epidemiology and Biostatistics, Norwegian School of Veterinary Science, Oslo, Norway
Copy held on file at UEA.

D. Nutrient Requirements of Fish and Shrimp (2011). National Research Council of the National Academies. National Academies Press (Washington DC). Histidine, p69.
Copy held on file at UEA.

E. Atlantic salmon – Deficiency diseases, Aquaculture Feed and Fertilizer Resources Information System, Food and Agriculture Organization of the United Nations (http://www.fao.org/fishery/affris/species-profiles/atlantic-salmon/deficiency-diseases/en/) Accessed 17/7/13 and held on file at UEA.

F. Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on the safety and the bioavailability of product L-Histidine monohydrochloride monohydrate for salmonids (2005, Question No EFSA-Q-2004-030)
The European Food Safety Authority Journal **195**: 1-10.
doi:10.2903/j.efsa.2005.195

G. Skretting Feed Catalogue 2013, p30.
Copy held on file at UEA.