Institution: Queen's University Belfast (QUB)

Unit of Assessment: 6 - Agriculture, Veterinary and Food Science

Title of case study: The Development of Vaccines for Porcine Circovirus Diseases

1. Summary of the impact (indicative maximum 100 words)

Postweaning multisystemic wasting syndrome (PMWS) had a huge global impact on the swine industry with estimated losses of €5-6 billion/year globally. Allan's team discovered and characterised the agent responsible for clinical development of PMWS (porcine circovirus 2 [PCV2]) and used these discoveries to drive vaccine development. The resultant PCV2 vaccines are the most successful ever produced for veterinary medicine and have: dramatically reduced global losses associated with PCV2 and other infections; improved pig health and welfare; and, reduced antibiotic usage. These vaccines are sold globally under licence and generate ~$600 million/year with 1.5% royalty income to QUB (2004-2018, ~$90 million).

2. Underpinning research (indicative maximum 500 words)

In 1996, the economic cost of PMWS (subsequently designated Porcine CircoVirus Disease [PCVD] or Porcine CircoVirus Associated Disease [PCVAD]) across the EU was ~€562-900 million because of fewer pigs at slaughter, reduced feed conversion rates, increased costs for management and medication of sick pigs. Although PCV2 infection alone is not zoonotic, the impact of PMWS on food safety and veterinary public health was also important as PMWS-associated immunosuppression results in increased carcase contamination by food-borne pathogens and increased shedding at slaughter, and an associated increase in the use of antimicrobial agents in the attempted control of PMWS-associated disease. Increased use of antimicrobials consequently increased the potential for selecting for antimicrobial resistant bacteria and drug residues in pig meat.

In 1996 Allan initiated studies at QUB (and The Department of Agriculture and Rural Development, DARD) with colleagues in the University of Saskatchewan (USASK), Canada and Merial Ltd., France to identify the causal agent of PMWS after unexplained outbreaks in North America and EU. Allan's team provided expertise in, and reagents for, porcine circovirus detection and growth in cell cultures and molecular biology expertise and the USASK team provided pathology expertise and material from diseased pigs. Merial provided funding and IPR expertise for the initial studies. Reagents and expertise were sent to USASK, including staff visits and samples of tissue from diseased pigs were sent to QUB. Samples from diseased pigs in the USA and Canada were processed in QUB and USASK using novel techniques through specially prepared cell cultures and assayed using immunohistochemistry for porcine circovirus (PCV) viral antigens and *in-situ* hybridization for PCV viral nucleic acid [**1**]. Using combinations of PCV-specific monoclonal antibodies (QUB), whole and partial PCV genomic probes (QUB) and, finally, whole genomic sequencing (QUB), a novel PCV virus (designated PCV2) was isolated from diseased pigs and PCV2 antigen and nucleic acid demonstrated in abundance in the lesions of infected swine [**2**,**3**] (USASK/QUB). Experimental infections of pigs by Allan's team and colleagues in the USA and Canada with PCV2 established, for the first time, that PCV2 was the infectious agent responsible for the full development of clinical PMWS [**4-6**]. IPR (QUB, USASK, Merial Ltd.) was filed on this new virus in 1997. Further IPR was filed in 1998 (16 patents filed so far) worldwide relevant to the IPR. Using the PCV2 isolate from Canadian pigs as the candidate virus QUB/USASK/Merial developed and tested a PCV2 vaccine which was eventually marketed in 2006/7. Following the launch of this initial vaccine, three other multinational companies developed PCV2 vaccines and these are marketed under licence to Merial.

In addition to the global amelioration of PMWS in swine, additional spin outs from the research by Allan's team include diagnostic test kits for PCV2, e.g. Serelisa CIRCO ELISA kit is on sale worldwide (1.5% royalties to QUB). Allan continues to work in QUB on PCV2 research and successfully co-ordinated three major EC consortia working on PCV2 and PMWS and involving over 22 partner institutes across the EU and North America.

3. References to the research (indicative maximum of six references)

***Publications on which the original PCV2 Vaccine IPR was based*:**

1. **Allan GM**, McNeilly F, Kennedy S, Daft B, Clark EG, Ellis JA, Haines DM, Meehan BM, Adair BM Isolation of porcine circovirus-like viruses from pigs with a wasting disease in the USA and Europe. 1998. *Journal of Veterinary Diagnostic Investigation* 10(1):3-10. [345 cites @180512]
2. Meehan BM, McNeilly F, Todd D, Kennedy S, Jewhurst VA, Ellis JA, Hassard LE, Clark EG, Haines DM, **Allan GM** Characterization of novel circovirus DNAs associated with wasting syndromes in pigs. 1998. *Journal of General Virology* 79(9):2171-9. [328 cites @180512]
3. **Allan GM,** McNeilly F, Meehan BM, Kennedy S, Mackie DP, Ellis JA, Clark EG, Espuna E, Saubi N, Riera P, Botner A Isolation and characterisation of circoviruses from pigs with wasting syndromes in Spain, Denmark, and Northern Ireland. 1999. *Veterinary Microbiology* 66(2):115-23. [173 cites @180512]
4. **Allan GM,** Kennedy S, McNeilly F, Foster JC, Ellis JA, Krakowka S, Meehan BM, Adair BM Experimental reproduction of severe wasting disease by co-infection of pigs with porcine circovirus and porcine parvovirus. 1999. *Journal of Comparative Pathology* 121(1):1-11. [287 cites @180512]
5. Ellis JA, Krakowka S, Lairmore M, Haines DM, Bratanich A, Clark EG, **Allan GM,** Konoby C, Meehan BM, Kennedy S, McNeilly F Reproduction of lesions of postweaning multisystemic wasting syndrome in gnotobiotic piglets. 1999. *Journal of Veterinary Diagnostic Investigation* 11(1):3-14. [211 cites @180512]
6. Krakowka S, Ellis JA, Meehan BM, Kennedy S, McNeilly F, **Allan GM** Viral wasting syndrome of swine: Experimental reproduction of postweaning multisystemic wasting syndrome in gnotobiotic swine by coinfection with porcine circovirus 2 and porcine parvovirus. 2000. *Veterinary Pathology* 37(3):254-63. [233 cites @180512]

Patents from Circovirus work:

- **Allan GM** et al. Porcine circovirus and paravovirus vaccine. US Patent 6217883; 17/04/2001
- **Allan G** et al. Porcine circovirus vaccine and diagnostics reagents. US Patent 6368601; 09/04/2002
- **Allan G** et al. Porcine circoviruses vaccines diagnostic reagents. US Patent 6391314; 21/05/2002
- **Allan G** et al. Porcine circovirus and parvovirus vaccine. US Patent 20020146431; 10/10/2002
- **Allan G** et al. Porcine circoviruses, vaccines and diagnostic reagents. US Patent 20020146432; 10/10/2002
- **Allan G** et al. Porcine circoviruses, vaccines and diagnostic reagents. US Patent 6660272; 12/09/2003
- Ellis J, **Allan G** et al. Reduction of porcine circovirus-2 viral load with inactivated PCV-2. US Patent 6517843; 02/11/2003
- Haines D, **Allan G** et al. Postweaning multisystemic wasting syndrome and porcine circovirus from pigs. US Patent 20040132178; 07/07/2004
- **Allan G** et al. Porcine circoviruses, vaccines and diagnostic reagents. US Patent 20040258715; 23/12/2004
- Ellis J, **Allan G** et al. Prevention of myocarditis, abortion and intrauterine infection associated with porcine circovirus-2. US Patent 20050058653; 17/03/2005
- **Allan G** et al. Porcine circovirus and parvovirus vaccine. US Patent 6953581; 10/11/2005
- Haines D, **Allan G** et al. Postweaning multisystemic wasting syndrome and porcine circovirus from pigs. US Patent 2006002952; 01/01/2006
- **Allan G** et al. Porcine circoviruses, vaccines and diagnostic reagents. US Patent 7122192;

17/10/2006
- Haines D, **Allan G** et al. Postweaning multisystemic wasting syndrome and porcine circovirus from pigs. US Patent 20060286642; 21/12/2006
- Haines D, **Allan G** et al. Postweaning multisystemic wasting syndrome and porcine circovirus from pigs. US Patent 20060292177; 28/12/2006
- Ellis J, **Allan G** et al. Prevention of myocarditis, abortion and intrauterine infection associated with porcine circovirus-2. US Patent 7211379; 01/05/2007

Research grants with G. ALLAN as PI and relevant to the PCV2 IPR:
- 1997-2003; Sponsor Merial. "Porcine Circovirus and PMWS" [£211,000]
- 1999-2002; Sponsor Imutran. "Circovirus and xenotransplantation" [£96,595]
- 2000-2003; Sponsor EU. Coordinator. "Novel circovirus infections of pigs and vaccination" [£215,000]
- 2002-2006; Sponsor Meat and Livestock Commission UK. “The role of colostrum and vertical transmission of viruses in PMWS disease development" [£60,143]
- 2001-2004; Sponsor Merial. "Immunisation strategies in young pigs" [£36,329]
- 2003-2006; Sponsor Higher Education Authority ROI. Coordinator "PCVD in Ireland" [£100,881]
- 2003-2008; Sponsor DEFRA/Warwick University. "Epidemiological studies on PMWS in the UK" [£114,720]
- 2005-2009; Sponsor EU. Coordinator "Control of PCVD: Towards improved food safety and quality" [£390,000]
- 2005-2009; Sponsor EU. Coordinator "New Member States and porcine circovirus disease (PCVD)" [£300,000]
- 2007-2011; Sponsor Republic of Ireland (DAF). STIMULUS FUND “Nutrition of farm animals for improved health and performance” [£138,888]
- 2008-2012; Sponsor Invest NI. “Development of nutritional products to ameliorate the effects of PCVD in swine” [£180,000]

4. Details of the impact (indicative maximum 750 words)

PCV2 has been associated with a number of disease syndromes or pathological conditions in pigs during the last 15 years, and the terminology ‘porcine circovirus diseases’ (PCVD) was proposed to replace existing acronyms. PMWS is considered the most significant PCVD, and therefore most of the prevention/control and research efforts have been focused on it. It is estimated that since its introduction in the 1990s, that PCV2 had cost the European industry about £468 million per year [**a**] and, at its height in 2005/6, it was estimated that PMWS cost EU pig producers in excess of €600-900 million per year. Subsequently, now that the disease has been reported in all major pig producing countries around the world, global production losses related to untreated PCVD are estimated in £billions per year. The impact of PMWS on food safety and veterinary public health is also important as PMWS-associated immunosuppression results in increased carcase contamination by food-borne pathogens and increased virus shedding at slaughter, and an associated increase in the use of antimicrobial agents in the attempted control of PMWS-associated disease. The latter provides an increased potential for selecting for antimicrobial resistant bacteria and drug residues in pig meat. PMWS and PCVDs are also important drivers of poor welfare in pigs.

The initial isolation and characterisation of PCV2 by Allan and colleagues at QUB, USASK and Merial, the filing of patents and the subsequent body of research that lead to an understanding of the disease process and development of diagnostics and vaccines, has been successfully deployed around the world to control this devastating disease [**b**]. Vaccines to PCV2 are now sold under licence by four multinational companies in all pig producing countries, with outstanding and unparalleled results. By October 2013, the associated royalty payments to QUB were is excess of US$32 million [**c**].

PCV2 vaccination has been one of the most extraordinary success stories of pig health control and is protecting the health, growth performance and welfare of many millions of pigs around the

world. No less importantly, the results at farm level show that it is more than fulfilling its promise to be extremely cost-effective and consumers are benefiting from a reduction in antibiotic use. The successful application of this vaccine against the diseases of major economic importance associated with PCV2 is internationally recognised. Launched in 2006, the PCV2 vaccine sales continue to increase year on year around the world with the estimates of market share in 2010 in Europe of 51%, North America at 73% and Asia at 67%. In 2008, world sales of PCV2 vaccines were valued at $265 million [**d**]. In 2012 IFAH-Europe (on behalf of the European animal health industry) reported that PCV2-vaccination is the only effective control for the PMWS [**e**]. As early as 2009, the major role played by PCV2 vaccination on reducing the on-farm use of antimicrobials had been recorded in Canada, Japan, South Korea, Thailand and UK [**f**]. The dramatic positive impact on pig farms, with mortality rates falling between 50 and 90% [**g**], has driven a year on year increase of PCV2 vaccine sales, making it the market leader [**h**]. The circovirus vaccines have delivered broad global impact and exceptional returns on investment [**i**]. In 2013, Boehringer-Ingelheim reported that one billion pigs had been vaccinated against PCV2 with Ingelvac CircoFLEX® and, **based on yearly sales volumes, that it is the most successful animal vaccine of all time [j].**

5. Sources to corroborate the impact (indicative maximum of 10 references)

a. http://www.wattagnet.com/Controlling_PCV2_and_other_major_pig_diseases.html
(16 March 2011: WATT Global Media report that since identification in the 1990s, it is estimated that PCV2 had cost the European industry about £468 million (US$749 million) per year.)
b. Letter from State Veterinarian, National Veterinary Institute, Sweden: (Confirms the impact of the Circovirus Vaccines in Sweden and the key role played by Gordon Allan, QUB.
c. October 2013: Summary of royalty payments, including those to QUB [highlighted yellow]).
d. http://www.pigprogress.net/Health-Diseases/Health/2010/2/PCV2-vaccination-changing-the-pig-industry---Part-2-Global-experiences-from-the-field-around-one-shot-vaccination-PP005994W/08
(February 2010: Pig *Progress* article describes global experiences from the field on PCV2 vaccine impact and cites that PCV2 vaccines achieved sales of $265 million in 2008.)
e. 21 June 2012: IFAH-Europe (representing European animal health industries) fact sheet on circovirus impact in pigs. (States that PCV2 vaccination is the only effective disease control.)
f. Glass (2010) PCV2 Vaccination Changing the Pig Industry. Pig *Progress* 26(2)
(2010: Pig*Progress* article reporting that PCV2 vaccines caused a reduction in antimicroibial usage across multiple countries.)
g. http://www.pigprogress.net/Home/General/2009/9/PCV2-vaccination-changing-the-pig-industry-PP005946W/
(01 September 2009: Pig *Progress* article reports how PCV2 vaccines are changing the pig industry and shows evidence that piglet vaccination reduces PCVD-associated mortality by 89%.)
h. http://www.thepigsite.com/swinenews/21120/world-swine-vaccine-market-driven-by-pcv2-vaccination
(19 May 2009: Boehringer-Ingelheim report that the size of the PCV2-vaccine market is close to €180 million and that Boehringer's Ingelvac CircoFLEX was the global market leader with total sales of ”€90 million last year.)
i. Letter from Merial's Head of Global Technical Services Swine (confirms the key role played by Gordon Allan in the development of PCV2 vaccines and the global scale of their impact on swine health and production as well as their exceptional return on investment.)
j. http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2013/14_february_2013ingelvac.html
(14 February 2013: Boehringer-Ingelheim reported that one billion pigs had been vaccinated against PCV2 with Ingelvac CircoFLEX® and, based on yearly sales volumes, that it is the most successful animal vaccine of all time.)