ARC • ANIMAL HEALTH RESEARCH CLUB

Supporting high-quality
industrially relevant research projects
on animal health and disease

www.bbsrc.ac.uk/arc

Animal Health Research Club (ARC)

Delivering global food security means providing a sustainable, secure supply of good quality food from less land and with more efficient use of inputs. Food security is a key strategic priority for the Biotechnology and Biological Sciences Research Council (BBSRC) and we are contributors to Global Food Security, a partnership bringing together the food related research interests of the relevant Research Councils, Government Departments, Devolved Governments and Executive Agencies.

Through discussions with industry, animal health has been identified as an area where targeted research is required. The cost of animal diseases to the UK economy can be very high– for example the 2001 outbreak of Foot and Mouth cost the UK £8bn and the long-term risk of dealing with exotic diseases costs UK industry approximately £100M per year. Resistance to disease has been highlighted as a priority area where increased investment in pre-competitive, innovative and industrially relevant research activity would underpin the capacity for the sector to tackle endemic and emerging pest and disease problems.

In line with its Business Interaction Strategy, BBSRC established the Animal Health Research Club (ARC) to bring together industry and the research community to support **research that improves our understanding of resistance to pests and diseases in farmed animals**. The club will generate knowledge and improve skills in the research community to provide valuable pre-competitive outputs for the animal breeding, pharmaceutical and production industry sectors.

This booklet provides information about the research challenges that are tackled through ARC funding, the benefits of industrial participation, and case studies of proposals that have been funded by the Club.

'The fifteen ARC projects are now up and running and cover a wide range of approaches to combating important infectious diseases of livestock. Several have established close links with industrial club members, with further links being promoted through regular dissemination meetings.

Projects address a range of livestock diseases caused by viral, parasitic and bacterial pathogens using state of the art technologies and current progress suggests that novel exploitable results will lead to new methods of disease control. Research is being directed at generating the tools to develop novel lines of sheep, cattle and poultry resistant to major diseases, to improve and develop vaccines and to understand complex diseases in order to implement improved interventions.

The Knowledge Transfer Nework (KTN) is delighted to see effective and interesting research taking place in ARC that reflects the needs of the industry.'

Andy Tait and Callum Harvey, Biosciences KTN

ARC Coordinators

Research Challenges

The focus of research funded through ARC is on improving the resistance of farmed animals to pests and disease and this includes cattle for beef and dairy, pigs, sheep, poultry and salmon. Projects address key challenges to industry through pre-competitive, innovative and excellent science.

Research on resistance to pests and diseases will help to ensure a secure supply of sufficient, safe and nutritious food for the benefit of the UK and internationally whilst contributing to reduced environmental impact and improved animal welfare.

ARC's research challenges are:

- Understanding the **basis of resistance/ resilience to pests and diseases** in farmed animal species
- **Developing novel tools** for defining disease biomarkers and phenotypes to inform breeding strategies for subclinical diseases and increased disease resistance
- **Understanding variation in vaccine responsiveness**, immuno-competence at different developmental stages and disease outcomes
- Determining the **effects of selection** for production traits on immune function

Industry benefits

Industry Benefits

Involvement in ARC provides industry partners with the following benefits:

- Opportunity to work with leading researchers
- Involvement in innovative research to support and strengthen the sector
- Access to new knowledge and tools
- Access to intellectual property arising from the research, to allow further development or commercial exploitation of results
- Exposure to a wider industrial and scientific network
- Information and advice relating to Research Council activities
- Public promotion and recognition through the initiative
- Opportunity to help foster succession in the Animal Health Research base and a pipeline of highly skilled recruits to industry

ARC has 12 company members who contribute to funding research and take part in directing the Club's activities. ARC has a total budget of approximately £9.5M:

£965k – Industrial membership subscriptions
£500k – The Scottish Government
£8M – BBSRC

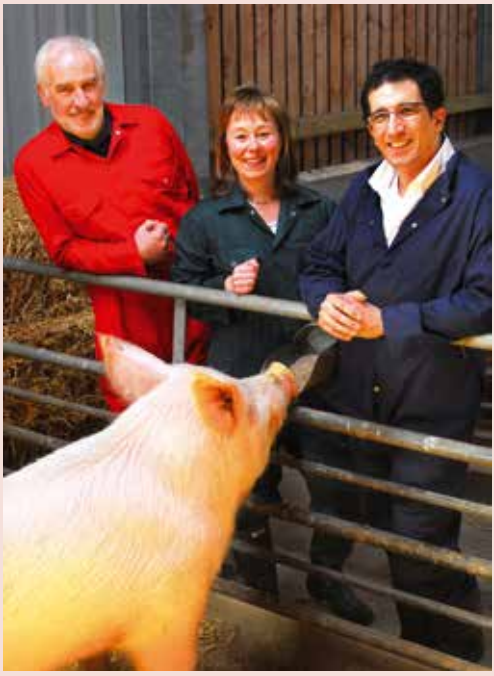
'The Animal Health Research Club is delivering a suite of projects across the dairy, beef, sheep and pig sectors that will provide science to underpin improved performance of livestock, contributing to the improved sustainability of our levy payers. We are excited to see the outcomes of this research and work with the research teams to deliver these into knowledge exchange for our industry.'

Chris Lloyd
Director of Research and Development and Knowledge Exchange (Livestock), AHDB

Engineering resistance to Porcine Reproductive and Respiratory Syndrome Virus (PRRSV)

Professor Alan Archibald, Professor, Bruce Whitelaw, Dr Simon Lillico and Dr Tahar Ait-Ali from The Roslin Institute, University of Edinburgh

Porcine Reproductive and Respiratory Syndrome (PRRS) is a viral disease of pigs that causes major economic losses. Whilst limited control has been brought about by changes in biosecurity and vaccination, PRRS still has major impacts on pig health and welfare and is the most costly disease to the pig industries worldwide. New PRRS virus (PRRSV) variants have demonstrated the potential to be even more devastating than endemic strains.



The ARC research team at the pig facility.
©*The Roslin Institute, University of Edinburgh*

PRRSV is a rapidly evolving small enveloped RNA virus which infects subpopulations of differentiated macrophages, with alveolar macrophages being the major target cells. There is convincing evidence for host genetic variation in responses to and outcomes of PRRSV infection. Thus, there is scope for genetically improving traits related to the capacity of pigs to tolerate or even totally resist PRRS infection and disease. Breeding for disease resistance is however constrained by the nature of the available genetic variation in susceptibility to infection. Whilst evidence for genetic variation in host responses to infection with PRRSV exists, the genetic control of these responses is polygenic and there is no evidence to date of major genes conferring complete resistance to PRRSV.

The increased efficiency and precision of methods to genetically modify farmed animals offers alternative approaches to generate animals which are genetically resistant to specific pathogens. The approaches to engineering resistance to a viral pathogen, such as PRRSV, include interfering with the receptor(s) through which the virus gains entry, viral uncoating or replication.

Are microbiomes important to mammary gland health in dairy cows?

Dr Kevin Purdy, Professor Laura Green, Dr Edward Mark Smith – University of Warwick
Professor Martin Green, Dr Andrew Bradley – University of Warwick

Mastitis, a bacterial infection of the udder (mammary gland), is the most common cause of disease and death in dairy cows. Each year around 50 % of cows suffer from mastitis and about 1 in 4 of these cows die or are culled. Mastitis is managed by good hygiene along with treatment and/or prevention with antibiotics administered via the teat when a cow stops milking.

© *Roberto Burgos*

Over 150 types of bacteria can cause mastitis with 5 types responsible for most cases. Understanding and developing vaccines for individual strains of bacteria, has not led to better control of mastitis or a reduction in mastitis occurrence.

Evidence exists that cows with udders that are already colonised by certain bacterial species are the least likely to suffer from mastitis. In these udders the bacteria present cause very little inflammation and do not reduce milk quality. It is not understood what happens that leads to cows changing from carrying low levels of apparently harmless bacteria in the udder and suffering no disease to then going on to develop mastitis.

Several species of bacteria living together (a community) are found in many sites of an animal's body and disease can occur when the balanced bacterial community is disturbed allowing one bacterial strain to dominate.

This research hypothesises that a natural community of bacteria exist in the cow udder before the cow is first suckled by its calf and that this community plays an important part in preventing mastitis. Modern molecular technologies have made it possible to detect and identify all the bacterial species present in a milk sample without having to grow them, researchers will investigate:

- At which time point bacteria can first be detected in the udders of young calves and heifers.
- How the bacteria in the udder change over time from when a cow is treated with antibiotics at the beginning of the dry period through to the birth of its next calf and for the following 4 weeks, the period when cows are most likely to get mastitis..

800 mammary gland quarter sample sets will be investigated to see how the microbial community forms and changes over time at drying off, with calving, milking, mastitis, and treatment with antibiotics and whether it remains stable if not disturbed by disease and treatment. Statistical analysis will be used to determine whether specific bacteria or combinations of bacteria help protect against mastitis, how antibiotics affect the management and control of the disease and produce ideas for new strategies to develop and maintain cow health and milk output and quality.

Selection versus mutation: reducing the risk of vaccine reversion

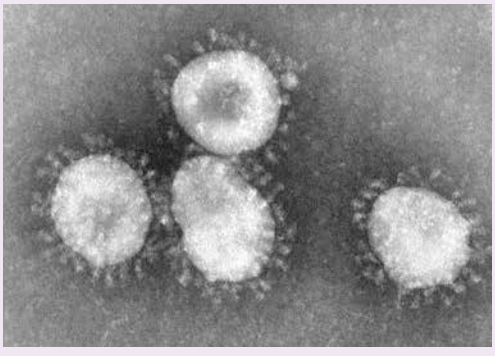
Professor Paul Britton and Dr John Hammond – The Pirbright Institute
Professor Daniel Haydon – University of Glasgow

Vaccination against infectious bronchitis virus (IBV), an endemic virus causing severe disease outbreaks in chickens, is essential in the poultry industry to prevent infection and ensure that the productivity of the industry remains above sustainable levels.

Effective and economically viable vaccines against IBV are mainly produced from pathogenic virus strains by passing in eggs approximately one hundred times. During these passages the virus accumulates multiple sequence variations from the original pathogenic sequence, leading to attenuation of the virus. These live attenuated vaccines have lost their ability to cause disease but still elicit a protective immune response in the chicken against future infection. As these are live viruses the potential exists for reversion back to a pathogenic form.

Understanding how different pressures influence the attenuation process is essential to the development of future vaccines and to reduce the threat of reversion. This study will use passaged pathogenic IBV strains produced in the same way as vaccines. In parallel a unique system that allows the passage of a single virus clone rather than a mixed virus population will also be used. Contemporary deep sequencing technology will be used to study, in fine resolution, the molecular changes occurring during the attenuation process. This will reveal, for the first time, how a mixed population of virus changes during vaccine manufacture and the extent to which individual viruses can mutate. These results will then inform a series of studies that manipulate the forces that drive virus change.

Ultimately this research will reveal how IBV is attenuated by egg passage and identify key regions of the genome that prevent the virus from causing disease but do not impair its potential as a vaccine. By understanding and manipulating the processes that govern virus attenuation and vaccine production, researchers aim to identify ways to reduce the danger of vaccine strain reversion that is responsible for damaging disease outbreaks.



Infectious bronchitis virus.
© CDC Public Health Image Library ID number 4814

'We welcome this Selection Versus Mutation initiative as one of the main concerns in the development of live vaccines is reversion to virulence. If after a long money consuming attenuation process your candidate vaccine virus appears to revert to virulence in your safety studies you need start from scratch again. Everybody will benefit if we would have better control on these processes.'

Harm Geerligs, Zoetis

Genomic selection for bovine tuberculosis resistance in dairy cows

Professor Liz Glass, Professor Stephen, Bishop, Professor John Woolliams – University of Edinburgh, The Roslin Institute, working with Professor Mike Coffey, Scottish Rural Colleges and Drs Robin Skuce, Adrian Allen and Stanley McDowell, Agri-Food and Biosciences Institute, Northern Ireland.

Despite over sixty years of costly eradication programmes, Bovine tuberculosis (bTB), a chronic respiratory disease caused by the bacterium, Mycobacterium bovis, remains an increasing problem in cattle herds in the UK and Republic of Ireland. bTB has major economic, trade, health and welfare impacts on the cattle industry worldwide and poses a risk to humans, other domesticated, feral and wild animal populations.

Eradication programmes include the slaughter of animals which are positive for a skin test which indicates bTB infection. Alternative control strategies are urgently needed as previous studies suggested that cattle differ genetically in their risk of bTB, opening up the possibility of genetic selection for decreased risk of bTB.

Breeding livestock for more favourable traits is becoming faster and more accurate through advances in genomic resources and information, including new genotyping tools such as high density single nucleotide polymorphism chips. These 'chips' consist of thousands of SNP markers which can relate variation across the genome to variation seen in traits. Researchers will conduct a meta-analysis of large datasets based on SNP chip genotypes linked to bTB phenotypes derived from statutory data from dairy cattle herds in the UK and Republic of Ireland. These will be exploited to develop genomic predictors of bTB infection which could then be directly applied by the cattle industry to select for bTB resistance.

The researchers will ensure that selection for bTB resistance is not detrimental to other desirable traits by determining the genetic relationship of bTB resistance with milk production and other economically important features.

Holstein Friesian dairy cows. © The University of Edinburgh used with the kind permission of The Roslin Institute, The University of Edinburgh.

By sequencing the genomes of individual cattle they hope to pinpoint the exact genetic changes which cause bTB resistance, improving the accuracy of the genetic predictors across generations. These results will enable scientists to explore the underlying basis for resistance to M. bovis infection, which could lead to designing better control strategies.

'Bovine tuberculosis (bTB) remains a seemingly intractable problem in the UK and a challenge to come up with new solutions. ARC has provided a great opportunity for us to take our research on genetics of bTB to the next stage - developing genomic predictors for bTB resistance in dairy cattle. This clearly defined practical outcome can potentially be directly applied by the cattle industry and could play a significant role in future control strategies.'

Professor Liz Glass, Principle Investigator

Restriction of avian viruses by host interferon-inducible transmembrane proteins (IFITMs)

Dr Mark Fife – The Pirbright Institute
Professor Paul Kellam – Wellcome Trust Sanger Institute

Global population growth and rising affluence are fuelling demand for poultry meat and eggs and a need exists to increase their supply. Poultry products are the main source of animal protein for human consumption worldwide and current global production is 55 billion chickens per year. The UK poultry industry contributes around £3.4bn to the UK economy.

Viruses that infect poultry have major effects on the global poultry industry through reduced outputs of poultry meat and eggs. Developing efficient viral control strategies is therefore crucial for the poultry industry and for alleviating poverty in developing countries where widespread disease causes devastating effects on poultry farming. Furthermore, controlling infections such as influenza in the avian host may directly impact on disease spread to humans.

Recent evidence revealed a family of proteins produced in human cells which can limit the entry and replication of several dangerous human viruses, including the flu virus. These proteins have been well characterised in human and mouse, but only limited details of two such proteins have been published in chickens; thought to be equivalent to two of the five known human proteins. Chickens or flocks with more active versions of the protein may be more resistant to avian influenza virus and other poultry viral diseases. Preliminary work established that the chicken versions of these proteins can protect against influenza infection. The aim of this proposal is to understand the biology and genetic changes of these genes in chickens. Specifically, the ability of the genes to protect the chickens against viruses will be examined. The output of this project will be identified versions of these proteins that give resistance to a number of avian viruses. Poultry breeding companies will then be able to select the protective version of the genes encoding these proteins in future breeding programmes.

'The proposed studies are highly relevant to BBSRC strategy on food security and meet the needs of the poultry industry, as reflected in the guidelines of the Animal Health Research Club, which includes world-leading poultry breeders. The project is an important, timely, and logical extension of recent work arising from our laboratories on the basis of genetically determined host resistance to viral infections. In this project will use our unique inbred chicken lines that are the subject of substantial infrastructure investment from BBSRC. Furthermore, the project offers valuable training in molecular, cellular and whole-animal approaches to unravel the basis of viral pathogenesis and protection.'

Dr Mark Fife and Professor Paul Kellam

Photo courtesy of Adam Ward

Understanding resistance and differential vaccine responses to *Eimeria* in the chicken – novel biomarkers and genetic control

Professors Pete Kaiser and Stephen Bishop – The Roslin Institute, University of Edinburgh
Dr Damer Blake and Professor Fiona Tomley – Royal Veterinary College

One of the main underpinning factors for a profitable large-scale poultry industry is the fact that the disease coccidiosis, caused by species of the protozoan parasite *Eimeria*, is controlled primarily through the use of drugs, or coccidiostats. Reliance on a single main control measure is not ideal, particularly with political pressure in some parts of the world to ban the use of coccidiostats. Vaccines are currently primarily produced by passage of *Eimeria* through birds and therefore are neither a cheap nor practical solution to replace coccidostats.

Resistance to *Eimeria* infection has recognised in inbred lines of chickens, but attempts to map this have been largely unsuccessful.

Eimeria maxima oocysts. USDA ARA PUBLIC DOMAIN

Chromosomes associated with resistance have been identified, but causative genes, or better still causative mutations, are yet to be identified. Differential responses to vaccines have been described, presumably due to similar mechanisms, but this has yet to be formally proven.

In this research, disease resistance and differential responses to vaccines will be mapped, using modern techniques, in particular the newly available 600K SNP chip. Similarly to BBSRC-funded work on *Campylobacter* resistance, both inbred birds in a backcross design and commercial birds in a genome-wide association study will be used.

It is well established that the control of *Eimeria* infection requires a strong inflammatory response, but the precise components of this response are not understood, as it was last studied in depth before details of the innate immune response and different T cell populations were known in the chicken. Researchers will therefore analyse the immune response to *Eimeria* infection. By investigating potentially novel aspects of this response the findings may lead to new tools for defining disease biomarkers and phenotypes.

The influence of selective breeding on MHC diversity

Professor Michael Stear, Dr Louise Matthews, Dr Richard Reeve – University of Glasgow

Animals differ in susceptibility to disease and much of the variation is genetic in origin. The major histocompatibility complex (MHC) is one of the most important genetic regions as it contains genes that determine how the immune system recognises and responds to disease-causing foreign organisms.

Animal breeders seek to identify genetically resistant animals and use these to produce offspring with enhanced resistance to disease. Evolution has produced a wide range of different genetic variants at the MHC and it is possible that this diversity can be managed to optimise disease resistance in livestock populations.

This project will identify the selective forces that maintain variation at the MHC, through a test system utilising parasitic roundworm, an important disease of livestock. It is known that the MHC plays an important role in roundworm resistance and the roundworm infection and disease process in sheep in particular, is well understood. This system is therefore ideal to study how MHC variation influences resistance to disease.

A population of sheep selected for high levels of roundworm resistance will be studied to allow quantification of the selective forces that maintain the high variation at the MHC. Using advanced statistical programs to remove background variation it will be possible to test whether roundworm resistance in individuals with different MHC genes could have arisen by chance.

Results from previous testing of a Scottish population led to predictions that individuals with a pair of similar genes will recognise fewer parasite molecules than an individual with a pair of dissimilar genes. It is expected that individuals that recognise more parasite molecules will be more resistant to infection.

The influence of selective breeding for disease resistance and production traits on MHC diversity will be measured using a recently developed mathematical formula to aggregate many different measures into a single diversity profile. The process of selection will also be modelled to reproduce the effect of selection on MHC diversity. Once an understanding has been developed of how selection affects MHC diversity and how MHC diversity affects disease resistance, selection schemes can be created to optimise the contribution of the MHC for resistance to disease.

'We are pleased that the Animal Health Research club has funded this work. The project aims to incorporate the most important set of genes for disease resistance into modern breeding practice.'

Professor Michael Stear, Principle Investigator

ARC membership

We thank all the ARC member companies for their input into the Club, both financial and scientific, and look forward to working with them over the course of the Club projects. We also thank the KTN for their coordination work, and The Scottish Government for their input and funding of the Club.

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Email: arc@bbsrc.ac.uk
www.bbsrc.ac.uk/arc
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