The Moredun Foundation
News Sheet Vol. 7 | No. 11 | August 2021

Moredun's Centenary Science Stories

Volume 4

Photo: www.pixabay.com

Professor Julie Fitzpatrick BVMS, MRCVS, MSc, PhD, DSc, FRAgS, OBE, FRSE
Moredun Research Institute

Photo: www.pixabay.com

introduction

As I write the introduction to the fourth and final volume of Moredun's Centenary Stories, I am aware that I have not covered all the breadth and depth of the research, development and innovation that has underpinned Moredun's success for more than a century. I am also concerned that I have not included stories on more recent initiatives in the organization including work on anti-microbial resistance, methods of reducing its impact, and even preventing it through development of alternatives, especially vaccines, rather than relying on drugs. Another principal area of focus for Moredun Research Institute is sustainable agriculture and especially livestock production. This is essential if Scotland is to meet its Climate Change Targets and of course, reduced waste in primary livestock production translates into better use of natural resources, improved productivity, and increased return in investment and profitability for livestock keepers. One of the pathways to success is to reduce the common infectious endemic diseases which in turn improves sustainability and animal health and welfare. That's what Moredun has always focused on!

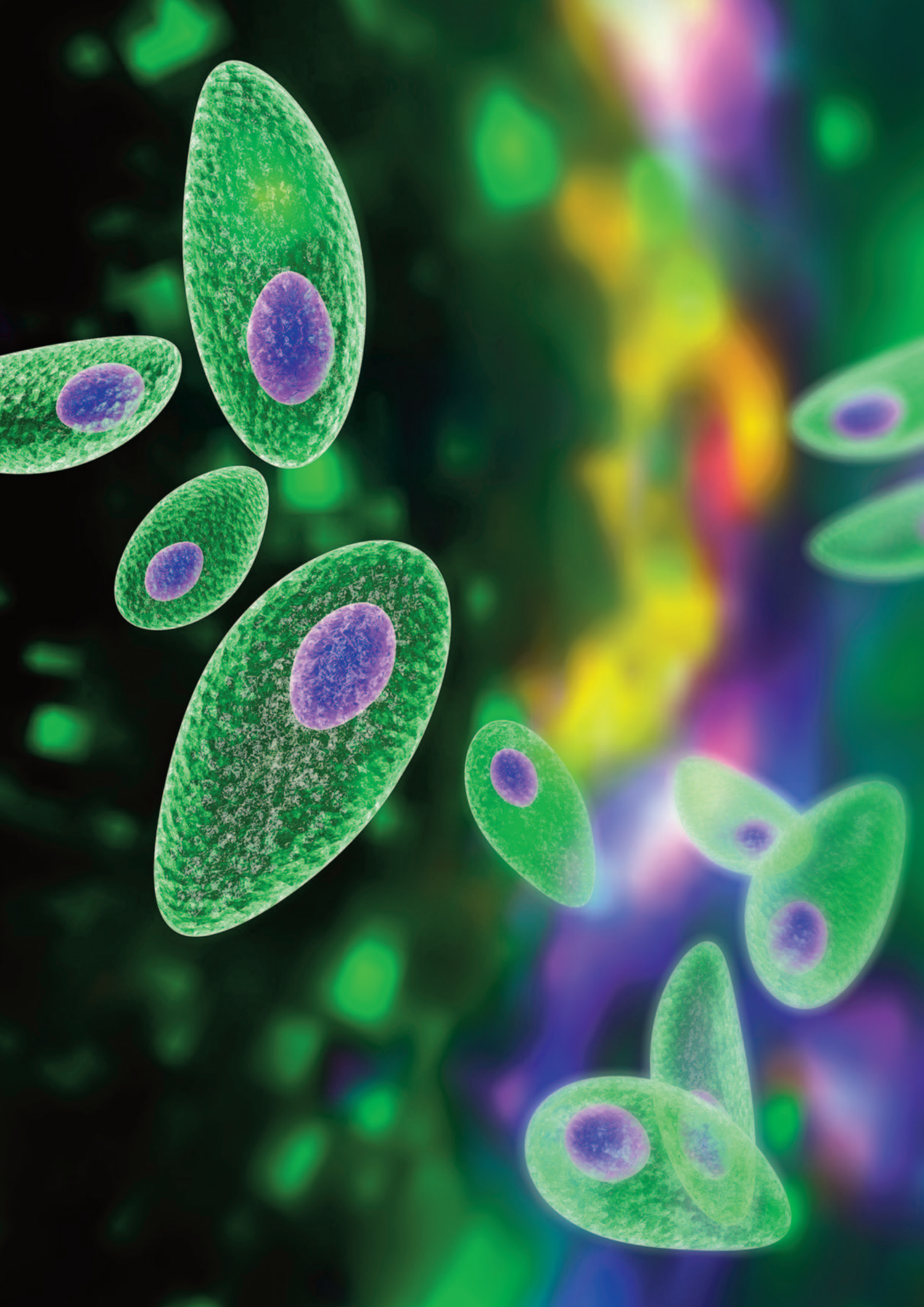
In some stories, I have referred to previous scientists employed at Moredun, while in others I have mentioned a small number of current staff and students. In all cases, the success of Moredun's science throughout the last 100 years is almost entirely down to the vision, skills, and sense of purpose of all the many staff who have contributed across the Moredun Group. I would also like to acknowledge the financial support from the Scottish Government in particular, via its many acronyms, now RESAS, for their ongoing commitment to longer-term strategic research which is the essence of our work.

In some of the stories included in this volume, I have tried to show why the subject matter is contemporary and where it fits with the current Global Grand Challenges we all face - Emerging infectious and zoonotic diseases, exemplified by the current COVID-19 crisis; endemic diseases adversely affecting welfare and reducing production efficiency, in turn impacting on Climate Change targets; food safety and security; and finding solutions to these problems including diagnostics, vaccines and disease control programmes.

The Moredun Research Institute has been able to maintain its contribution to policy relevant research regionally, nationally and internationally through its focus specifically on identifying and diagnosing infectious diseases and commitment to developing solutions to address them. This has led the drive for Moredun scientists to work closely with industry including the animal health and biotechnology sectors across the world. Commercial outputs from these efforts includes attracting co-funding from public and private funds, building patent portfolios, selling on technology for others to commercialise or manufacture, and even establishing spin-out companies.

The Centenary Stories have focussed specifically on Moredun Research Institute's work, however, the Moredun Foundation has two fully owned commercial subsidiaries, Moredun Scientific and Pentlands Science Park. These two companies are essential for the scientific and financial success of the whole Moredun Group, as when they create profits, these are gift-aided to the Foundation and then onto the Institute, providing extra income to undertake more research and development for livestock health and welfare. This creates a virtuous cycle for ongoing investment and exemplifies Moredun as a public-private partnership. Pentlands Science Park, as the name suggests, is a science park with 22 tenants most of whom are involved in agriculture, environment and biotech activities. It is one of the first science parks in the world to be built around a livestock health institute. Moredun Scientific undertakes contract work that includes testing the efficacy of livestock vaccines and therapeutics for EU registration and this work has continued unabated since the UK's exit from the EU. Moredun Scientific's recent efforts have included checking many of the COVID-19 commercial vaccines for biosafety, indicating the connectivity between biology of animal and human species. This is but one example of the One Health initiative that has continued to gain traction during the current COVID-19 pandemic. You will see some examples of the Moredun Research Institute's research on zoonotic diseases, those which transfer from animals to humans, in this volume, followed by closing comments from Moredun's Communications Director, Professor Lee Innes. I hope you enjoy these final stories!

Professor Julie Fitzpatrick
Scientific Director and Chief Executive



Toxoplasmosis

Feline species are the definitive host of Toxoplasma gondii. Insert: T. gondii bradyzoite.

"*Toxoplasma gondii*, is probably the most successful parasite worldwide," is a sentence regularly quoted by Professor Elisabeth (Lee) Innes and her colleagues, as 1 in 5 people worldwide are thought to be infected. While research has helped to elucidate some of the complexities of this parasite and the diseases it causes, there remains much to be done if the impact of this parasite is to be reduced in both livestock and human populations.

T. gondii is a protozoan organism (a single-celled microscopic parasite) with a complex lifecycle that results in the disease toxoplasmosis. Understanding the lifecycle of the parasite is important for recognising routes of infection among species and identifying potential means of control. The starting point is known to occur within the gut of members of the cat family (Felidae), where the parasite reproduces and forms eggs known as 'oocysts'. The oocysts are subsequently shed in faeces into the environment. Cats are the only known species where this occurs, making them the definitive host of the parasite – *T. gondii* cannot survive without them.

Experimental studies led by Dr David Buxton at Moredun in the late 1980s, established the infective dose required to reproduce the clinical and pathological effects of *T. gondii* infection in pregnant ewes and their foetuses or lambs. It was found that *T. gondii* could be isolated from the foetuses of ewes challenged at various stages of pregnancy around 10 days after infection. The protozoa would invade the pregnant uterus and cause local damage, followed by disruption of the placental tissues ([1]Buxton and Finlayson, 1985). This study also showed that while foetuses did not produce a significant immune response until 20 days post-infection, they became increasingly able to do so from 70 days post-infection. These results helped to explain why toxoplasmosis caused stillbirth or abortion when infection occurred in early and mid-pregnancy, while foetuses of ewes infected later were more likely to survive the infection - although lambs were often born weak and subsequently died.

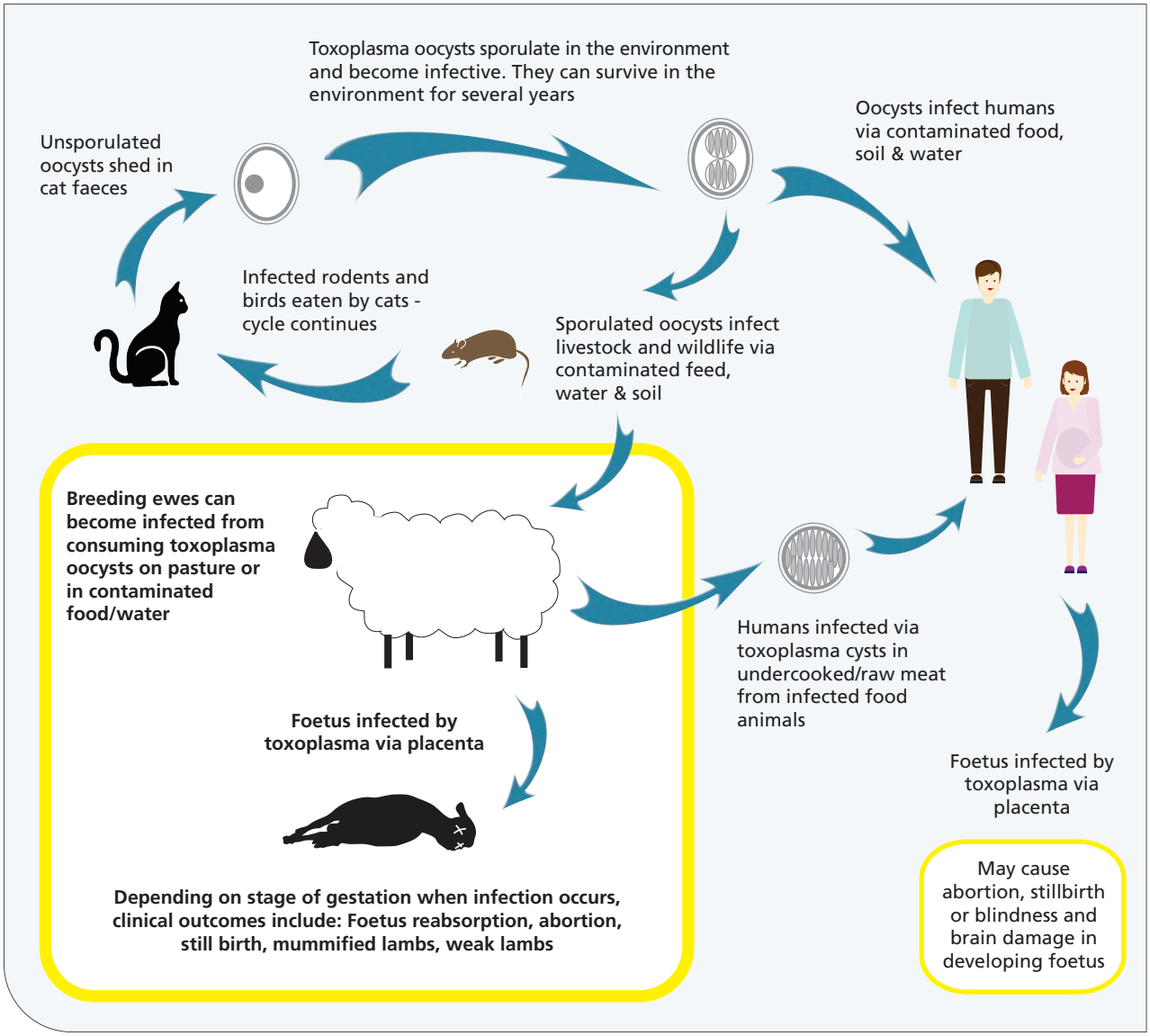


Fig. 1: Life cycle of T. gondii: The three different stages of the parasite (oocysts, tissue cysts and tachyzoites) are transmitted by either: 1) horizontal transmission of oocysts from the environment; 2) horizontal transmission from tissue cysts within intermediate hosts; and 3) vertical transmission of tachyzoites from mother to foetus during pregnancy. Adapted from Hunter and Sibley. Nature Reviews Microbiology 2012 Nov; 10:766-778.

Moredun played a key role in developing the first commercial vaccine for toxoplasmosis in the UK. The 'S48 vaccine' was a live, incomplete strain of *T. gondii* tachyzoites – the rapidly dividing and invasive developmental form of the protozoa (see Fig. 1). Efficacy trials of pregnant ewes showed that 75% of ewes vaccinated with S48 prior to mating produced lambs, which were both live and viable. However, unvaccinated ewes produced only 18% of lambs which were live and viable following challenge with *T. gondii,* with the majority producing aborted foetuses or dead or unviable lambs ([2]Buxton and Innes, 1995). The vaccine was able to induce long lasting protection, predominantly produced by T cells (white blood cells that make up an important component of the immune system) indicating the importance of cell mediated immunity to protect against this disease.

Studies indicated that the T cells induced by the infection had a long immunological 'memory', explaining in part why live vaccines for *T. gondii* are more effective than killed vaccines.

Detailed investigation of the cellular immune response of vaccinated sheep in real time was achieved through the analysis of lymph fluid using a surgical cannulation technique. This identified that a subset of T cells called CD8 T cells, associated with killing pathogens inside cells, was the dominant immune response detected around the time when *T. gondii* parasites disappeared from the lymph fluid, emphasising the importance of cell mediated immune responses in protective immune responses. Work continues in scientific centres around the world, including at Moredun, and approaches for vaccination against *T. gondii*

remain paramount. A review paper by [3]Innes et al (2019) calls for a collective effort in using a One Health approach to vaccination to tackle this important zoonotic disease.

The parasite can also be transmitted to people through the consumption of undercooked meat from food animals infected with *T. gondii* tissue cysts. The World Health Organisation and European Food Safety Authority have highlighted *T. gondii* as one of the most important food borne pathogens worldwide, emphasising the importance of Moredun's work to help prevent and control the disease in livestock.

Another method of transmission of *T. gondii* is water-borne, leading to Moredun's involvement with public health bodies in developing methods to recover *T. gondii* oocysts from water supplies and extracting DNA from them. Studies by [4]Wells et al (2015) compared the use of two polymerase chain reaction (PCR) tests in identifying *T. gondii* DNA and found approximately a third of 1427 samples from 147 water supplies across Scotland were positive. The intriguing question remains: Are domestic cats responsible for seeding infection in so many sites across Scotland, including remote areas with water reservoirs, or could there be a role for their wildcat relatives?

Little information was available on the level, or prevalence, of *T. gondii* in the human population of Scotland, so Moredun scientists embarked on a study on serum (the liquid part of blood) from samples taken from over 3000 human blood donors over 4 years. ELISA tests, which measure antibodies, indicated that 13.2% of donors had antibodies to *T. gondii,* similar to levels reported in other parts of the UK and Europe. A small number of donors had blood samples which were originally negative but found to be positive at later sampling dates. This indicates 'sero-conversion' to *T. gondii,* where the antibody has had time to develop and become detectable in the blood.

The second sampling study was of human brain tissue via collaboration with the Medical Research Council Sudden Death Brain and Tissue Bank, which holds tissues from patients who died suddenly and had no underlying disease conditions. In this case, the tissues were examined for evidence of *T. gondii* infection using PCR tests to identify the DNA of the protozoa. 17.9 % of brains were shown to be positive for *T. gondii* DNA ([5]Burrells et al, 2016). In both the blood samples and brain studies described above, an increase in age was associated with an increase in detection of *T. gondii,* indicating acquired infection – in other words, people were exposed to *T. gondii* and developed antibodies throughout their lives, suggesting ongoing exposure to the parasite.

Some Moredun scientists are fortunate when their research takes them to foreign parts, none more so than Dr Clare Hamilton who was based in the Caribbean between 2014-2016. It had recently been recognised that South America had a high level of atypical strains of *T. gondii,* which caused severe clinical outcomes in humans. The study involved collecting and genotyping Caribbean isolates of *T. gondii* from livestock species and comparing them to a virulent Brazilian strain and an avirulent European strain in a mouse model of infection. Results showed that virulent Caribbean strains were similar to the Brazilian strain in terms of genotype (DNA); however, proteins produced by the two strains differed, suggesting complex pathways of *T. gondii* relating to virulence and effects on humans ([6]Hamilton et al, 2019).

Toxoplasmosis, which can cause lesions in the brains of humans, has been associated in some studies with poor cognitive ability and some forms of mental illness, and work is required to identify how often this happens and how it might be prevented. If you look again at the lifecycle in Figure 1, you will see that the transmission cycle requires cats to eat mice with the bradyzoite (slowly dividing tissue-based stage) of *T. gondii,* which then goes on to produce oocysts in the cat's intestines. Studies of *T. gondii* infections in mice have shown that mice tend to lose their fear of cats – a sure way of continuing the ongoing success of the parasite!

I would like to thank Professor Lee Innes and Dr Clare Hamilton for their help in developing this story.

References:

1. Buxton, D., Finlayson, J. (1986). Experimental Infection of Pregnant Sheep with *Toxoplasma gondii*: Pathological and Immunological Observations on the Placenta and Foetus. Journal of Comparative Pathology 96(3):319-333. https://doi.org/10.1016/0021-9975(86)90052-6
2. Buxton, D., Innes, E.A. (1995). A Commercial Vaccine for Ovine Toxoplasma. Parasitology 110: S11-S16. https://doi.org/10.1017/S003118200000144X
3. Innes, E.A., Hamilton, C., Garcia, J.L., Chryssafidis, A., Smith, D. (2019). A One Health Approach to Vaccines Against *Toxoplasma gondii*. Food and Waterborne Parasitology 15: e00053. https://doi.org/10.1016/j.fawpar.2019.e00053
4. Wells, B., Shaw, H., Innocent, G., Guido, S., Hotchkiss, E., Parigi, M., Opsteegh, M., Green, J., Gillespie, S., Innes, E.A., Katzer, F. (2015). Molecular Detection of *Toxoplasma gondi*i in Water Samples from Scotland and a Comparison Between the 529bp real-time PCR and ITS1 nested PCR. Water Research 87:175-181. https://doi.org/10.1016/j.watres.2015.09.015
5. Burrells, A., Opsteegh, M., Pollock, K.G., Alexander, C.L., Chatterton, J., Evans, R., Walker, R., McKenzie, C.A., Hill, D., Innes, E.A., Katzer, F. (2016). The Prevalence and Genotypic Analysis of *Toxoplasma gondii* from Individuals in Scotland, 2006–2012. Parasites & Vectors 9:324. https://doi.org/10.1186/s13071-016-1610-6
6. Hamilton, C., Black, L., Oliveira, S., Burrells, A., Bartley P.M., Melo, R.P.B., Chianini, F., Palarea-Albaladejo, J., Innes, E.A., Kelly, P.J., Katzer, F. (2019). Comparative Virulence of Caribbean, Brazilian and European Isolates of *Toxoplasma gondii*. Parasites and Vectors 12(1):104-114. https://doi.org/10.1186/s13071-019-3372-4

Barbervax

Barbervax is the first ever commercial vaccine against a nematode worm worldwide. Development of the vaccine was far from straightforward however, and this story takes many twists and turns. Barbervax protects sheep and goats against infestation by a worm called *Haemonchus contortus*, which lives in the abomasum, or fourth stomach. The female worm is about an inch long and is easily visible to the naked eye. Its uterus is white but its blood-filled gut is red and twisted around it, thus resembling a barber's pole, which still adorn many barbers' shops today. Hence, when the Moredun Research Institute-owned company, Wormvax, was established, the choice of vaccine name was obvious.

The vaccine was first registered in Australia in 2014 where it is manufactured to Good Manufacturing Practice in collaboration with Dr Brown Besier and colleagues at Department of Primary Industries and Regional Development, Western Australia. The vaccine was first field trialled in 2013 when four farmers agreed to try out the vaccine in their Merino flocks in New England, the epicentre of *Haemonchus* country due to warm, wet springs and summers, exacerbated by high levels of resistance to all the commonly used anthelmintic drugs. In these areas, the impact of *Haemonchus* can be very severe indeed as this worm sucks blood from the lining of the abomasum, with large numbers of worms resulting in severe anaemia and sudden death in lambs and ewes.

The real test of a vaccine is in the field under commercial conditions and it was clear that Barbervax was going to be a success when these initial farmers were very keen on using the vaccine in repeated seasons after being involved in the trials.

Local Merino lamb producer in New England, Brian Lanz, said "Barber's pole is our single biggest challenge and we have resistance to a lot of drenches. Costs of using Barbervax were on par with our normal program, but we expect longer-term savings and will definitely be using it again next season. It's a terrific breakthrough for our industry."

In the first year of using Barbervax, the Smiths from Kentucky in New South Wales (who both have full time off farm jobs) used it with young sheep only. The following year, they used it more broadly and now every sheep on the property is vaccinated. They said, "Barbervax vaccine was a godsend for managing barber's pole worm."

The story begins some decades ago when Moredun Research Institute's scientists Dr David Smith, Dr George Newlands and co-workers first identified the molecule H-gal-GP as the vaccine antigen ([1]Smith et al, 1994). This vaccine antigen, extracted from the surface of the worm's gut, is a complex of enzymes, which break down proteins digesting the worms' blood meals. As the vaccine antigen is extracted from the worm tissues, it is termed a native protein and as the inside of the worms' guts are not exposed to the general immune system of the sheep, it is also called a hidden antigen.

Initial trials, conducted in New South Wales in 2007 were promising ([2]LeJambre at el, 2008). When H-gal-GP was used as a vaccine in one group of grazing lambs, then compared to another unvaccinated groups of lambs, the vaccinated sheep had lower numbers of *Haemonchus* eggs in their faeces and higher levels of antibody in blood samples than the control group. None of the vaccinated sheep required treatment with anthelmintics and the level of pasture contamination was reduced. The authors concluded that if a recombinant (an artificially designed protein) version of H-gal-GP could be made then a commercial vaccine was a real possibility.

Studies were undertaken in many countries and with a number of different livestock species through well-established collaborations. Barbervax was shown to be effective against *Haemonchus* in goats ([3]de Matos et al, 2017) and in cattle infested with a similar parasite *Haemonchus placei* ([4]Bassetto et al, 2014) both in Brazil.

Several years later, multiple recombinant versions of the vaccine antigen had been tried and failed, much to the disappointment of the Moredun parasitology team. However the "Eureka" moment came when it was found that as little as two millionths of a gram of the native form of H-gal-GP was effective, suggesting that it might be viable to make a commercial vaccine derived from worm material.

Work started in Western Australia where commercial lambs destined for routine slaughter were deliberately infected with *Haemonchus* and their abomasums recovered at the nearby abattoir. Kilograms of clean worms were then harvested from them using Nem-E-Sys, a patented worm-extraction machine, homogenised and the relevant antigens isolated using protein chemistry methods. This approach provides millions of doses of Barbervax cost-effectively.

Photo: www.pixabay.com

It was always very frustrating that it was not clear as to why it has proven impossible to produce a recombinant version of the vaccine antigen. Collaborations with scientists at the University of Leeds using cryo-electron microscopy, mass spectrometry and molecular modelling allowed visualisation of the H-gal-GP complex and it was very complex! The molecule has a central digestion chamber, an arch and two wings which according to the modelling could wave about ([5]Scarff et al, 2020). This confirmed the expectation that the vaccine antigen was a structure embedded in the lining of the worm gut. Haemoglobin and albumin, the most abundant proteins in blood, fit into the digestion chamber but antibody induced by the vaccine would block their entry, hence preventing digestion of the blood meal and starving the worms to death - a Trojan horse approach! Another fascinating aspect of this work is that a similar molecular complex to H-gal-GP was found in the guts of other worm species including *Ostertagia ostertagi* which affects cattle and the hookworm, *Ancylostoma ceylanicum*, which infests humans and dogs. This suggests the intriguing possibility of a pan-nematode vaccine in future!

At the time of writing, Barbervax is on sale in Australia and South Africa and can be obtained by veterinary prescription in the UK. There is great interest in bringing the vaccine to South America, especially Brazil and Uruguay, both large sheep-rearing countries. *Haemonchus* is also being increasingly recognised as a problem in European countries and in the south of England. Barbervax can be imported under special license to meet these demands.

I would like to thank Dr David Smith for help in developing this story.

References:

1. Smith, W.D., Smith, S.K., Murray, J.M (1994). Protection studies with integral membrane fractions of *Haemonchus contortus*. Parasite Immunology 16(5): 231-41. https://doi.org/10.1111/j.1365-3024.1994.tb00345.x
2. LeJambre, L.F., Windon, R.G., Smith, W.D. (2008). Vaccination against *Haemonchus contortus*: Performance of native parasite gut membrane glycoproteins in Merino lambs grazing contaminated pasture. Veterinary Parasitology 153(3-4): 302–312. https://doi.org/10.1016/j.vetpar.2008.01.032
3. de Matos, A.F.I.M., Nobre, C.O.R., Monteiro, J.P., Bevilaqua, C.M.L., Smith, W.D., Teixeira, M. (2017). Attempt to control *Haemonchus contortus* in dairy goats with Barbervax®, a vaccine derived from the nematode gut membrane glycoproteins. Small Ruminant Research 151:1-4. https://doi.org/10.1016/j.smallrumres.2017.03.016
4. Bassetto, C.C., Silva, M.R.L., Newlands, G.F.J., Smith, W.D., Ratti Junior, J., Martins, C.L., Amarante, A.F.T. (2014). Vaccination of grazing calves with antigens from the intestinal membranes of *Haemonchus contortus*: effects against natural challenge with *Haemonchus placei* and *Haemonchus similis*. Int J Parasitol 44(10): 697–702. https://repositorioslatinoamericanos.uchile.cl/handle/2250/927223?show=full
5. Scarff, C.A., Thompson, R.F., Newlands, G.F.J., Jamson, A.H., Kennaway, C., da Silva, V.J., Rabelo, E.M., Song, C.F., Trinick, J., Smith, W.D., Muench, S.P. (2020). Structure of the protective nematode protease complex H-gal-GP and its conservation across roundworm parasites. PLoS Pathogens 16(4): e1008465. https://doi.org/10.1371/journal.ppat.1008465

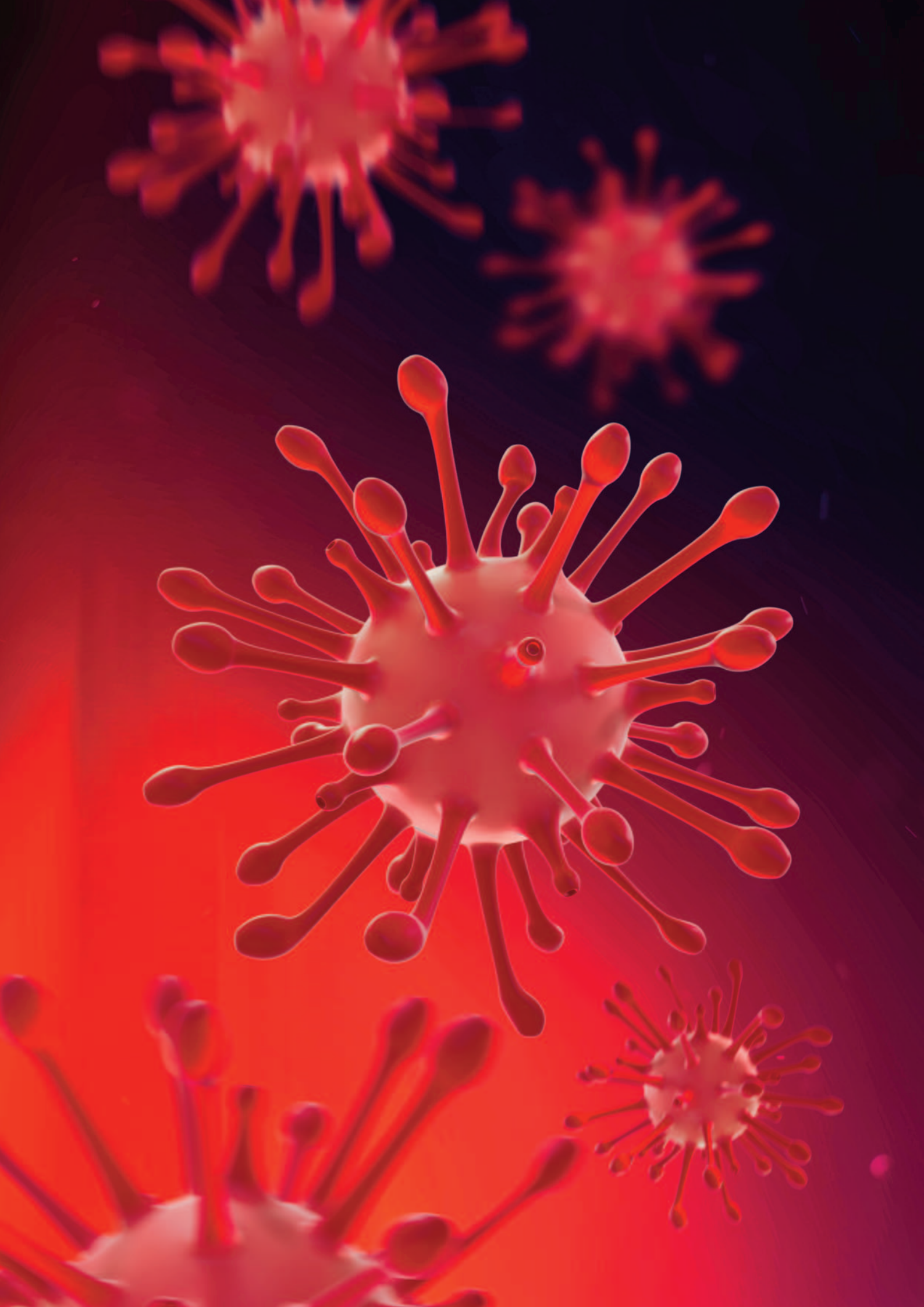


Photo: www.shutterstock.com

Moredun's Response to the COVID-19 Pandemic

Photo: Janina Costa

Scientists busy at work testing for SARS-CoV-2.

In March 2020, COVID-19 was spreading rapidly in Europe and the UK and there was an urgent need to develop and deploy diagnostic tests to quickly identify infected individual people and reduce the spread of the infection in the human population. The molecular real-time polymerase chain reaction (RT-PCR) test to detect SARS-CoV-2 was found to be a sensitive and reliable test to detect individuals with the virus. This molecular diagnostic test was chosen to be deployed within the National Health Services Scotland's clinical diagnostic laboratories throughout the country.

At this time, Professor Elisabeth Innes of Moredun contacted the NHS to offer help in expanding testing capacity and to provide support in the national emergency. As there was no clear communication route, various academic networks were contacted and it took a bit of persistence and following up leads to eventually make contact with a group led by Dr Ingólfur Johannessen, Director of NHS Lothian Laboratory Medicine and Clinical Lead for the Scottish National Laboratory Medicine Programme. This was a critical contact as Dr Johannessen was co-ordinating the development of academic nodes to help expand the capacity of testing for SARS-CoV-2 in collaboration with the NHS diagnostic laboratories.

The project, which was then launched, was a huge success for all involved. Moredun and SRUC were the first national veterinary facility to perform SARS-CoV-2 RT-PCR testing and the project is a great example of One Health in action.

The testing node went live on 25th June 2020, initially offering a 5 days a week service that was increased to 7 days a week during the second wave of the pandemic over the winter period. A total number of 34,764 samples were tested from hospitals, care homes and other health boards across Scotland. Staff volunteers from both institutes, 19 from Moredun and 14 from SRUC, were trained to conduct the testing. Six new staff were recruited to Moredun and 3 new staff to SRUC, providing excellent training and employment opportunities for recent graduates.

The testing node ceased the service to the NHS on 2nd July 2021, as the NHS transferred testing to 3 large regional hub laboratories.

The excellent collaboration between Moredun, SRUC and NHS and the contribution the project made to help tackle the Covid-19 pandemic in Scotland was recognised as the team were shortlisted as finalists in the Scottish Knowledge Exchange Awards 2021.

SARS-CoV-2 Research at Moredun

One of the most recognisable features of the SARS-CoV-2 virus are the spikes sticking out from the core of the organism. When these spikes are viewed by electron microscopy, a method involving very high magnification, the virus appears to have a crown, or corona, as a result of the outward projecting spikes, and hence the name, coronavirus (see Fig. 1). The spikes have a very important function in initiating the infection process as they make contact with the animal or human tissues, especially cells in the respiratory tract. The spike protein is also important as this is where the mutations (random genetic changes) which have resulted in the variants of concern take place. These mutations have the potential to change the efficacy of diagnostic tests and of vaccines - although fortunately this is not the case for the available commercial vaccines at the time of writing in the current COVID-19 pandemic.

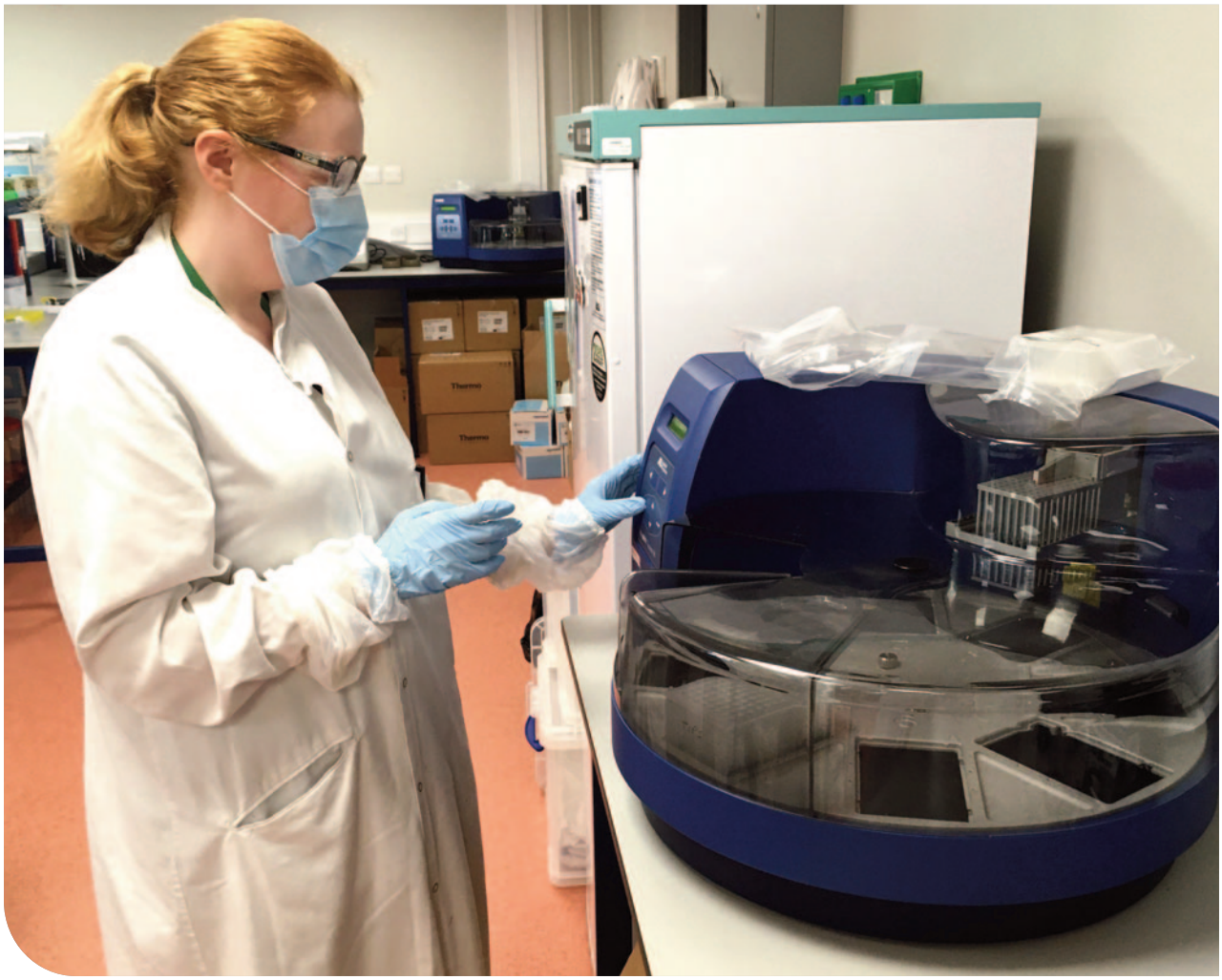


Photo: Jenny Thacker

Photo: www.shutterstock.com

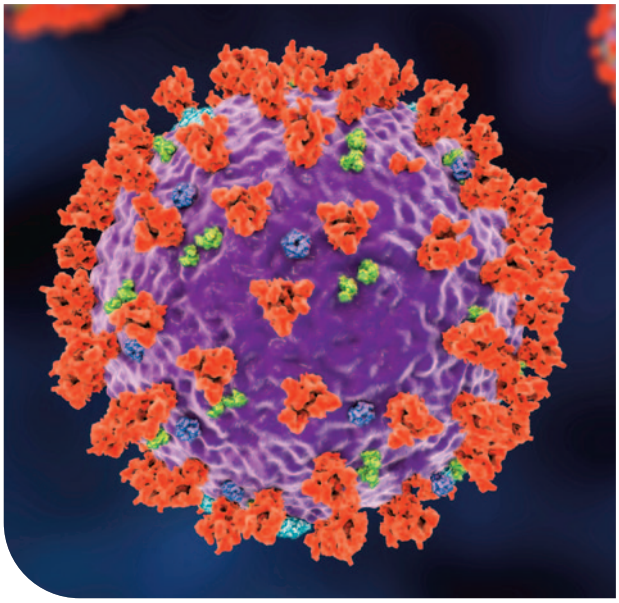


Fig. 1 The SARS-CoV-2 virus showing the "spikes."

Dr Tom McNeilly led a project at Moredun with colleagues from the Roslin Institute and the Queen's Medical Research Institute, University of Edinburgh. They had developed a transgenic mouse strain, one that produced the human receptor for SARS-CoV-2 in its tissues and organs, rather than the mouse version of the receptor. When these mice were infected with SARS-CoV-2 by introducing the virus into the respiratory tract, the mice developed clinical signs of disease and had significant pathological changes in lung tissues at *post-mortem* similar to those found in COVID-19 affected humans. This particular project is another example of the versatility of scientists who focus on infectious diseases be they of animals or humans. This work was also only possible because of Moredun Research Institute's specialised animal facilities and scientific staff, essential for the safe conduct of this work.

Dr David Griffiths and colleagues at Moredun Research Institute rapidly developed serological assays for use in detecting antibodies to SARS-CoV-2. Two fragments of the Spike glycoprotein of SARS-CoV-2 were produced by recombinant (artificially constructed) methods in cell lines in the laboratory, which were then purified and used to immunise two sheep and two cattle. All four animals responded strongly by developing antibody against the recombinant proteins. The scientists also established an assay for detecting antibodies that were able to kill or neutralise the virus. Again all four immunised animals showed this ability. These reagents and assays are valuable tools that will underpin planned infection studies with SARS-CoV-2 in livestock and mice and an ongoing serological survey that will assess whether ruminants can act as a minor reservoir species for SARS-CoV-2.

As the PCR testing was underway and tests for antibody immune responses were being developed in the laboratory, Moredun was approached by collaborators across Scotland who were interested in investigating SARS-CoV-2 in animals. Establishing if viruses are able to infect animals is a very important step to understanding how the virus produces its damaging effects. It also allows creation of animal models which can then be used to test if novel drugs or other biological products can reduce the severity and duration of infection, or even prevent it altogether - the aim of vaccine studies.

I would like to thank Professor Lee Innes, Dr David Griffiths, Dr Mara Rocchi and Dr Tom McNeilly for their help in developing this story.

Photo: Mara Rocchi

Photo: www.pixabay.com

Louping Ill

Photo: www.pixabay.com

This story focuses on one of Moredun's most iconic diseases - louping ill. By way of interpretation for those not used to the Scottish vernacular - to "loup" is to jump or spring into the air, describing the movements of affected sheep caused by damage to their nervous system, targeted by the louping ill virus (LIV). The virus is transmitted by ticks, which act as a vector in that they transmit LIV to animals and people through their bites. The tick species involved is called *Ixodes ricinus* and it is very common in Scotland, as many will be aware. There is evidence of tick presence in wider geographical areas of the country, which may result from warmer, wetter conditions associated with climate change and the increased movements of animals with their ticks attached!

LIV affects sheep, red grouse, deer and mountain hares and these iconic animal species are important for food production and for biodiversity in the upland and hill areas of Scotland's estates, moors and farms. The virus is also zoonotic in that it can transmit from animals to humans, although fortunately clinical disease in people is uncommon.

Photo: www.shutterstock.com

Scientists at the Moredun Research Institute developed an inactivated (killed) vaccine based on LIV antigen recovered from cells cultured in the laboratory. When the antigen was mixed with oil, as an additional stimulant (or adjuvant) a single dose of the vaccine induced a strong antibody response in the blood of vaccinated sheep. This antibody was shown to be able to neutralise and kill the virus. Results of a field trial conducted at Moredun and in collaboration with the Scottish Veterinary Investigation Service, showed that again, vaccinated sheep mounted a strong antibody response after one dose of vaccine and that they were completely immune to LIV when exposed to natural infection on farms, which were known to be the home of the tick vector. In contrast, 29% of unvaccinated control sheep, which had been exposed to the same pasture and surroundings as the vaccinated sheep, died with clinical and pathological changes of LIV infection. Another important bonus was that vaccinated sheep maintained on farm for a second season were shown to pass on that immunity to their next lamb crop due to transfer of antibodies in colostrum ([1]Brotherston et al, 1971). This work formed the basis for a commercial vaccine that was used to control louping ill for over 30 years.

One of the risks of working with LIV was that researchers occasionally became infected with the virus. The expected causes and resulting clinical signs of three such cases were reported by [2]Reid at al, (1972). The causes included a needle-stick injury, a cut hand or close working with equipment that had been used to mash up tissue, followed by exposure to LIV infected tissue. All cases had fever, dullness and only one had a headache. Fortunately no neurological signs were presented. The diagnosis was confirmed by virus isolation from blood samples, followed by specific identification of LIV. This study, although it followed unintentional exposure to virus, provided much information about the progression of infection in humans.

New technologies to investigate viruses were applied to study 22 isolates of LIV from across the UK and collected over a period of 80 years! This involved whole genome sequencing (WGS) of the isolates, which allows comparisons of the similarities and differences among them. This work demonstrated that there were clusters of LIV strains in various geographical areas suggesting local transmission of virus and also evidence of long distance movements. The sequencing also suggested that LIV is genetically relatively stable with low rates of mutations (random changes in genes) and it was not possible therefore to create a molecular clock for LIV which is used for other viruses to indicate the speed of genetic changes ([3]Clark et al, 2020). Lack of information on the molecular clock of LIV may be due to the reliance of the virus on the tick vector with possibly long intervals between transmission events, in addition to the alternation of LIV in animal hosts or ticks. Viral replication and evolution of LIV in ticks, which are usually at ambient temperature, unless they have just feasted on blood from an animal, may be different to those that occur in warm-blooded animal species.

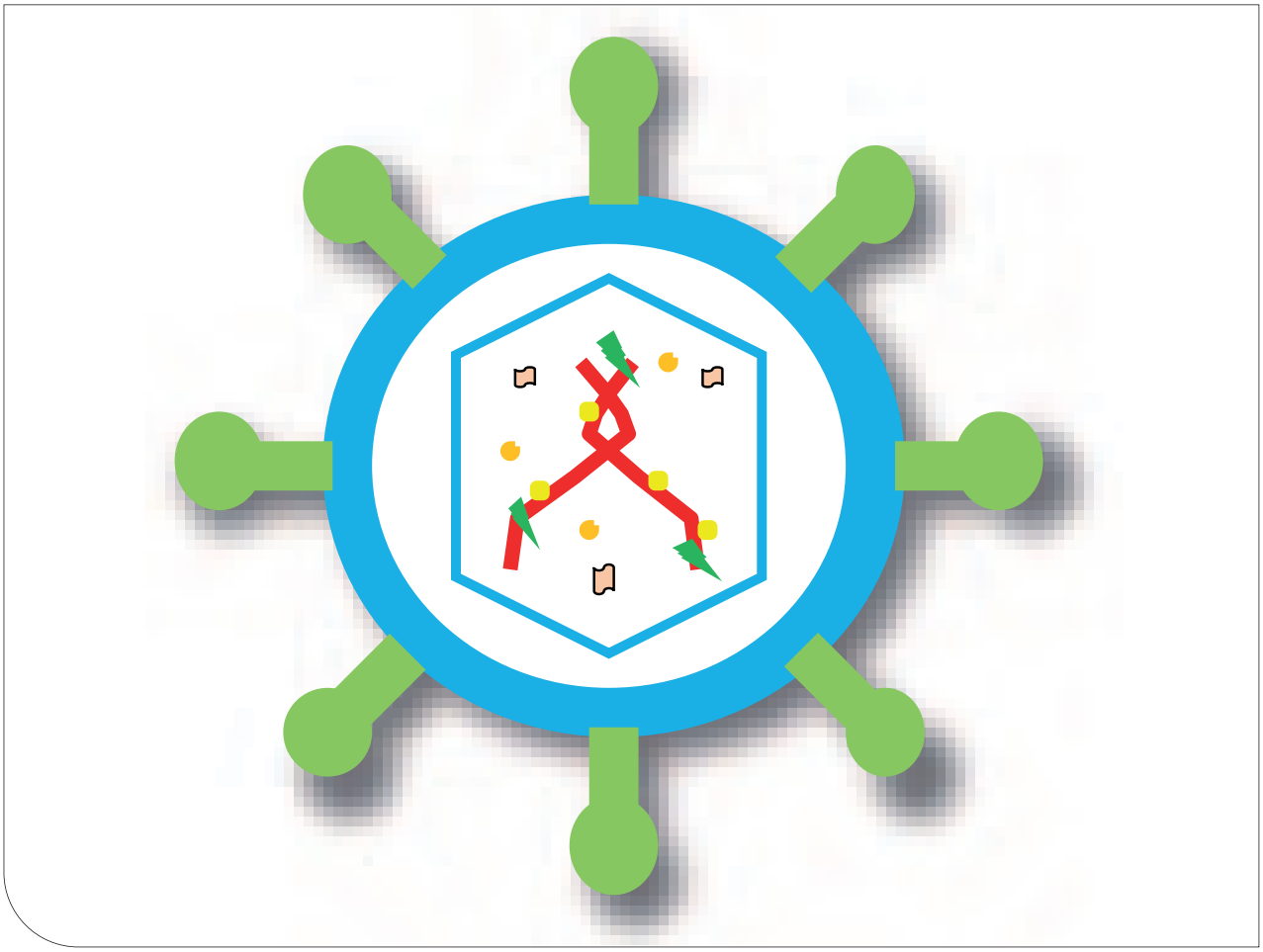


Diagram: David Griffiths

Diagram of the vector particle being used in the development of a new generation vaccine against LIV.

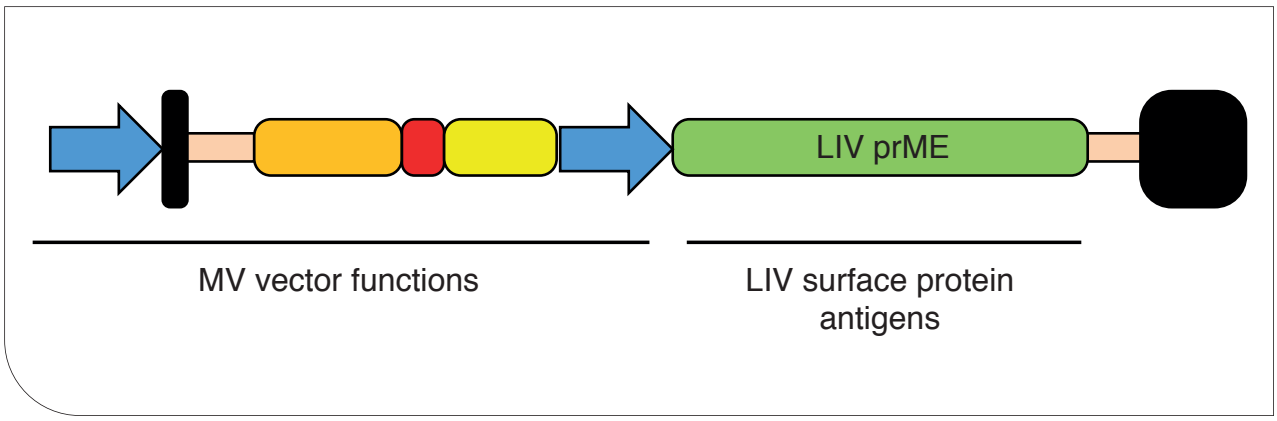


Diagram: David Griffiths

Diagram showing the development of a viral vector vaccine approach.

Louping Ill vaccine was produced commercially for many years and was extremely important for livestock farmers and estate managers in the areas affected by LIV. Unfortunately, problems with vaccine production resulted in gaps in supply, followed by cessation of commercial production.

Moredun scientists were able to step in to address this gap in vaccine production. Two approaches are currently under investigation. The first exploits methods that have been developed to insert genes for various infectious agents into viruses, which then act to transfer those genes into the tissues and cells of an animal species following injection - so called viral-vectored vaccines.

In this instance, protein antigens isolated from the surface of LIV were inserted into the virus causing Maedi-Visna, as shown above. The virus carrier is not able to replicate in the animals receiving the vaccine and so there is no risk of Maedi-Visna in the vaccinates. Initial studies were very encouraging in that sheep vaccinated in this novel way showed a very strong level of antibody in blood, far higher than was usually seen following the traditional commercial vaccine.

In the second approach, a vaccine comprising a recombinant (artificially constructed) version of the same LIV antigen is also under trial at Moredun.

It is envisaged that one of these approaches will lead to a new commercial vaccine in the coming years. This work has been generously funded by the Game and Wildlife Conservation Trust, through donations from Scottish Estate owners, and builds on the substantial research conducted with funds from the Scottish Government over many years.

Photo: www.pixabay.com

When the Moredun Foundation's Honorary President, John Cameron, was asked about his view on the most impactful research output from Moredun over the years, he said with no hesitation - "the louping ill vaccine!"

I would like to thank Dr David Griffiths for help in developing this story.

References:

1. Brotherston, J.G., Bannatyne, C.C., Mathieson, A.O., Nicolson, T.B. (1971). Field trials of an inactivated oil-adjuvant vaccine against louping-ill (arbovirus group B). Journal of Hygiene 69(3): 479-489. https://dx.doi.org/10.1017/S0022172400021732
2. Reid, H.W., Gibbs, C.A., Burrells, C., Doherty, P.C. (1972). Laboratory infections with louping-ill virus. Lancet 299(7750):592-593. https://doi.org/10.1016/S0140-6736(72)90385-6
3. Clark, J.J., Gilray, J., Orton, R.J., Baird, M., Wilkie, G., da Silva Filipe, A., Johnson, N., McInnes, C.J., Kohl, A., Biek, R. (2020). Population genomics of louping ill virus provide new insights into the evolution of tickborne flaviviruses. PLoS Neglected Tropical Diseases 14(9): e0008133. https://doi.org/10.1371/journal.pntd.0008133

Controlling Immunity

Moredun Research Institute's scientists have been instrumental in understanding immunity against multiple infectious diseases and some of these have been described in the Centenary Science Stories in this and previous volumes. One important aspect of immunity is how it is controlled genetically.

The Major Histocompatibility Complex (MHC) is a group of genes which are associated with the main branches of the immune response – antibody (humoral immunity) and cell-mediated immunity, including T and B cells amongst others.

Professor Peter Doherty, a PhD student at Moredun at the time, worked on louping ill virus (LIV (see the Centenary Story "Louping-Ill" in this current volume)) with Dr Hugh Reid and Charlie Burrells. The laboratory techniques involving LIV infection of cell lines were key to subsequent work which would lead to his Nobel Prize with Professor Rolf Zinkernagel on MHC restriction, awarded in 1996 ([1]Reid et al, 1972). These studies identified that the products of MHC genes were important elements that determined how T cells responded to pathogens both in the first exposure and the enhanced response to subsequent exposure. This was relevant both to re-exposure to the same pathogens and also to re-exposure to pathogens following vaccination.

The function of the MHC is important as it presents antigens, small proteins called peptides, to receptor molecules on T cells which are key regulators of the immune response. The MHC has a 3-dimensional shape into which peptides fit, thus the complex is like a lock while the peptide resembles a key. It is the interaction with this lock and key which then stimulates cell mediated immunity which in turn helps B cells to produce antibodies.

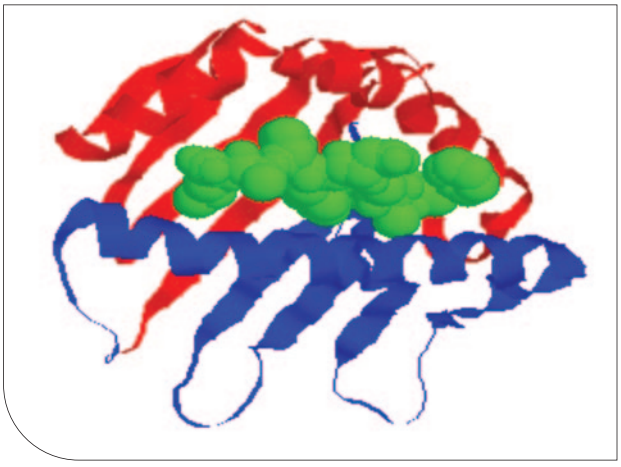


Diagram of the MHC complex.

The MHC is very diverse – different genes are present in different locations within the complex and studies indicated that this varied between livestock species, within families and between individuals ([2]Ballingall, et al, 1992). These studies progressed over the last 30 years to a stage where much of the vast diversity at the key MHC genes in all the major livestock species has been defined and this information is freely available to scientists worldwide through the immunopolymorphism database (IPD-MHC, https://www.ebi.ac.uk/ipd/mhc/).

This diversity protects populations, as when outbreaks of infectious diseases occur there is likely to be a significant proportion of individuals who are able to respond to a specific pathogen and hence the whole group are not decimated. Some livestock species and breeds which lack MHC diversity, which can be further exacerbated by inbreeding, have been shown to be vulnerable to disease or to have shortened lifespans.

MHC diversity has also been associated with differences in susceptibility to diseases in many livestock species ranging from Marek's disease in chickens to gastrointestinal nematodes in sheep and cattle. These types of studies require the genotyping of large numbers of animals in diseased and healthy populations.

Photo: www.pixabay.com

Photo: www.pixabay.com

New next generation sequencing tools now allow rapid population based analysis of all the key MHC genes from hundreds of animals in a single experiment. These technologies will contribute to ongoing work on the conservation of genetic diversity in livestock breeds and aid in defining pathogen proteins that stimulate protective immunity ([3]Maccari et al, 2017).

Studies on the MHC have linked to a number of projects conducted at Moredun. These include the identification of MHC class I genes in placental tissues of pregnant sheep ([4]Wattegedera et al, 2019); MHC class II genes in sheep vaccinated with Barbervax (see Centenary Story on Barbervax in the current volume); while specific antigens from *E. coli* O157:H7 were recognised by T-cells isolated from lymph nodes close to the rectum of cattle where *E.coli* adhere, from multiple animals with different MHS types.

The research on MHC is therefore important at one level in designing vaccine antigens through knowledge of how they fit with the immune regulatory molecules of different animals, and also at another level, their role in wider applicability to disease monitoring, diagnostics and selective breeding for the future.

I would like to thank Dr Keith Ballingall for help in developing this story.

References:

1. Reid, H.W., Gibbs, C.A., Burrells, C., Doherty, P.C. (1972). Laboratory Infections with louping-ill virus. Lancet 299(7750): 592-593. https://doi.org/10.1016/S0140-6736(72)90385-6
2. Ballingall, K., Wright, H., Dutia, B., Howard, J.C., Puri, N., Haig, D. (1992). Expression and Characterisation of Ovine Mhc class II Genes (OLA-DR). (1992). Animal Genetics 23:347-359. https://www.research.ed.ac.uk/en/publications/expression-and-characterization-of-ovine-major-histocompatibility
3. Maccari, G., Robinson, J., Ballingall, K., Guethlein, L., Grimholt, U., Kauffman, J., Ho, C.S., de Groot, N., Flicek, P., Bontrop, J.H., Marsh, S. (2017). Nucleic Acids Research, 45, Database issue D860–D864. https://doi.org/10.1093/nar/gkw1050
4. Wattegedera, S.R., Doull, L.E., Goncheva, M.I., Wheelhouse, N.M., Watson, D.M., Pearce, J., Benavides, J., Palarea-Albaladejo, J., McInnes, C.J., Ballingall, K., Entrican, G. (2019) Immunological Homeostasis at the Ovine Placenta May Reflect the Degree of Maternal Fetal Interaction. Frontiers in Immunology 9:3025. http://dx.doi.org/10.3389/fimmu.2018.03025


OLYMPUS
CKX41
7193

All Creatures Great and Small

Photo: Arpat Ozgul

Moredun has conducted research on numerous diseases of all types of animal species over the last century. In the first few decades, the Institute worked on understanding the causes, treatment and prevention of conditions such a milk fever (low blood calcium or hypocalcaemia) in cattle, and pine in sheep. Pine produced chronic signs of ill-thrift, poor production and reproduction as a result of low levels of trace elements, including cobalt, available on pasture. As the years went by, Moredun focused more closely on infectious diseases, caused by a variety of pathogens and pests, as these were most important in terms of animal welfare, loss of productivity and farm profitability. This focus remains in place today and is encompassed in Moredun's vision and strategy.

This story makes a brief account of only a small number of examples of the breadth of Moredun scientists' contribution to many animal species and their fascinating diseases.

Photo: Arpat Ozgul

Soay sheep

Soays have populated the St Kilda archipelago in the Western Isles of Scotland for thousands of years, free from management breeding or veterinary care. A number of scientific groups have studied this population of sheep, including those at the Moredun Research Institute.
To enable us to do this, the ethics of this work has been carefully considered by the Animal Welfare and Ethics Review Group at Moredun. One of the reasons for this is that the sheep are not subject to the usual veterinary interventions such as those that would normally prevent disease and its detrimental effects. The Scottish Government considers the Soay sheep as wild animals and Moredun conducts collaborative research, along with other researchers, on this basis.

Photo: Arpat Ozgul

Moredun scientists were involved in a very interesting study that looked at the role of infection, immunity and demographics using the Soay sheep as a model animal population. The work indicated a decline of immune resistance with old age in Soay sheep and identified some of the mechanisms involved. Results were published in Science, one of the highest ranking journals internationally ([1]Froy et al, 2019). Soay sheep are exposed to high levels of nematode parasites (common gut roundworms of multiple species) on St. Kilda. Measurements of antibody against multiple worms in blood samples taken from approximately 800 sheep were investigated to see if levels of antibody were consistent with later life immunosenescence (ageing of immunity) and if these were linked to parasite burden, bodyweight and subsequent mortality. Results showed that a reduction in anti-worm antibody declined in adults of both sexes as they approached death, in spite of female sheep outliving male sheep by some years. Interestingly, a particularly rapid decline in antibody was distinguishable in the final year approaching death. Study of this wild/self-limiting population of ruminants allows relevant comparisons with the managed livestock populations which have been long established in farming systems in Scotland and further afield, giving us a better understanding of immunity to disease and how to maximise the productive life-span of our farmed livestock.

Another study focussed on the predicted trade-off between reproductive effort and parasite-specific immunity in the Soay population. This indicated that high reproductive effort can limit the ability of individuals to defend themselves against common parasites, with potential downstream consequences for fitness and transmission of parasites among the animals ([2]Hayward et al, 2019).

Rabbit haemorrhagic disease (RHD)

RDH is caused by a calicivirus of the genus Lagovirus, rabbit haemorrhagic disease virus (RHDV). It was first recognised as an epidemic disease in China in 1984 where it killed hundreds of millions of rabbits in approximately one year, then spread rapidly across the world, including to Europe.

At the end of the summer of 2010, a new variant of the virus (initially called RHDVb, then RHDV2 or Lagovirus GI. 2) was detected in France, causing high mortality in domestic and wild rabbit populations. This quickly spread to neighbouring nations such as Italy and Spain in 2011 and to Portugal in 2012. The first detection of this variant in England and Wales was reported in March 2014, although the virus is now known to have been present in the UK since 2010. Moredun scientists became involved in the early diagnosis of the disease in April 2014 when the first Scottish case was diagnosed in a commercial rabbit breeding colony. Moredun's Virus Surveillance Unit (VSU) continued to provide molecular diagnostics via a polymerase chain reaction (PCR) test, which identifies virus genetic material, between 2015 and 2017, when a commercial test was introduced (see map detailing positive cases detected between 2014 and 2017). Moredun's VSU still support UK-wide wildlife surveillance. Genome sequencing confirmed that this was indeed a new virus, termed RHDV2. The origins of RHD viruses are not completely understood but they might have emerged from avirulent caliciviruses that circulate asymptomatically in rabbits.

In June 2020, wild rabbits in Wales were found to be dying in large numbers and at *post-mortem*, the rabbits did not have the extreme signs of classical RHD, but did have enlargement of the spleen. Moredun scientists became involved again in the disease investigation through collaboration with the Welsh Veterinary Science Centre, where samples were studied by electron microscopy, which allow visualisation of viruses through magnification and molecular testing. Genome sequencing confirmed the presence of RHDV2 in the rabbit livers ([3]Duff et al, 2020).

Since 2010 RHDV2 has gradually replaced the original RHDV strain in wild and domestic rabbit populations in the UK, as had already occurred in many other countries. RHDV2 infects brown hares as well as rabbits and wild species are at risk of transmission of infection to domestic rabbits and vice versa. There has been a decline of more than 50% in the UK rabbit population in recent years and the impact of RHDV2 on this decline is unknown. This indicates the impact of newly emerging viruses and their variants in epidemics causing novel disease and in this case, emphasises the importance of biosecurity across species.

Rabbits and their role in research approaches and disease transmission appear in a number of other Centenary stories including those on Johne's disease and transmissible spongiform encephalopathies (TSEs).

Photo: www.pixabay.com

Diagram: Mara Rocchi

UK map denoting positive cases of RHDV2 between 2014 and 2107.

Aquaculture

Moredun Research Institute embarked on research and development into the aquaculture space in 2012. This was stimulated by the importance of infectious diseases in both cold and warm-water fish, including those caused by parasites, viruses and bacteria, and the requirement to reduce reliance on drugs for treatment and prevention, with vaccination seen as the way forward.

Scotland has a thriving aquaculture sector worth approximately £885 million and based on the farming of Atlantic salmon (*Salmo salar* L.). Among a number of important diseases of salmon is cardiomyopathy syndrome (CMS) where the heart tissue is damaged by a number of viruses including piscine myocarditis virus (PMCV), resulting in either sudden death due to heart failure, or a more chronic form of debilitating disease. It has proved difficult to diagnose this condition at an early stage and before clinical signs are obvious, therefore Moredun scientists are developing an approach to identifying proteins in the blood of CMS-affected fish as potential early diagnostic markers. A study was conducted to identify these markers by taking blood samples from both diseased and normal, unaffected fish and comparing the panel of proteins of both populations using mass spectrometry (a method of identifying small proteins and their component building blocks, amino acids). Results showed that CMS-affected fish produced different proteins to normal fish, including those associated with leakage of proteins in heart tissues, similar to disease markers in humans with cardiac disease. This is an example of comparative medicine showing similarities in disease processes in animal species as different as fish and humans! The diseased fish also had different proteins involved in the inflammatory response which can be an aspect of both immunological (protective) or pathological (damaging) reaction to viruses, and in proteins which are involved in repair of damaged tissues ([4]Costa et al, 2021).

Photo: www.shutterstock.com

Atlantic salmon farm off the west coast of Scotland.

Photo: Kim Thompson

Nile tilapia farmed in Vietnam.

On the opposite side of the world, red tilapia is considered a very important fresh water species for global food security. Intensification of tilapia farming has resulted in increased prevalence of the bacterium *Flavobacterium columnare*, the causative agent of columnaris disease. Working with collaborators from Thailand and Japan, Drs Kim Thompson and Janina Costa were involved in a study investigating the performance of a novel vaccine against this disease. The vaccine was a biomimetic-mucoadhesive nanovaccine, broadly translating into a vaccine where the potential vaccine antigens are incorporated into extremely small particles (nanovaccines), which had been shown to attach strongly to mucous surfaces including the skin and gills of diseased fish (mucoadhesive) and which has similar biological shape and properties, although not infectious, as the original bacterium (bio-mimetic). This is an example of the increasingly bio-engineered forms of modern vaccines. Another interesting aspect of this work is that the vaccine was administered to fish by immersion in water, with the fish absorbing the vaccine antigen via tissues including the gills. This research provided encouraging results with fewer deaths occurring in the vaccinated fish than the unvaccinated group, with the relative percentage survival of vaccinates being 78% ([5]Kitiyodom et al, 2021).

Photo: Kim Thompson

A Nile tilapia farm near Hue, Vietnam.

Equine Grass Sickness

The Moredun Foundation has been responsible for holding the Equine Grass Sickness Fund since 1988 and is honoured to have had Her Royal Highness The Princess Royal as its patron since 1990.

Horses were extremely important in the early years of the Animal Disease Research Association (ADRA), the inaugural name of the Moredun Research Institute, as they were literally the power-house of farming in their role as draught animals for ploughing and general farm work. Of course, in Scotland, many of these heavy horses were magnificent Clydesdales. They, along with other horse and pony breeds, were susceptible to an illness that mainly affects horses with access to pasture, hence the name Equine Grass Sickness. ADRA scientists were involved in investigations right from the start of the organisation, publishing in 1944, a twenty year review on the clinical signs and histo-pathology (microscopic changes caused by the disease) findings of horses affected by Grass Sickness. This review described in meticulous detail the observations made during life, followed by changes in the organs of the body *post-mortem* ([6]Holman et al, 1944). The authors published this paper to provide evidence of the lack of clear histo-pathological changes in tissues with the exception of general congestion in the stomach and gut. These were because of the fluid accumulation in the stomach and impaction of the bowel, which resulted in the serious clinical signs in both acute (sudden) and chronic (slow) respectively, manifestations of the disease.

Photo: Alison Burrells

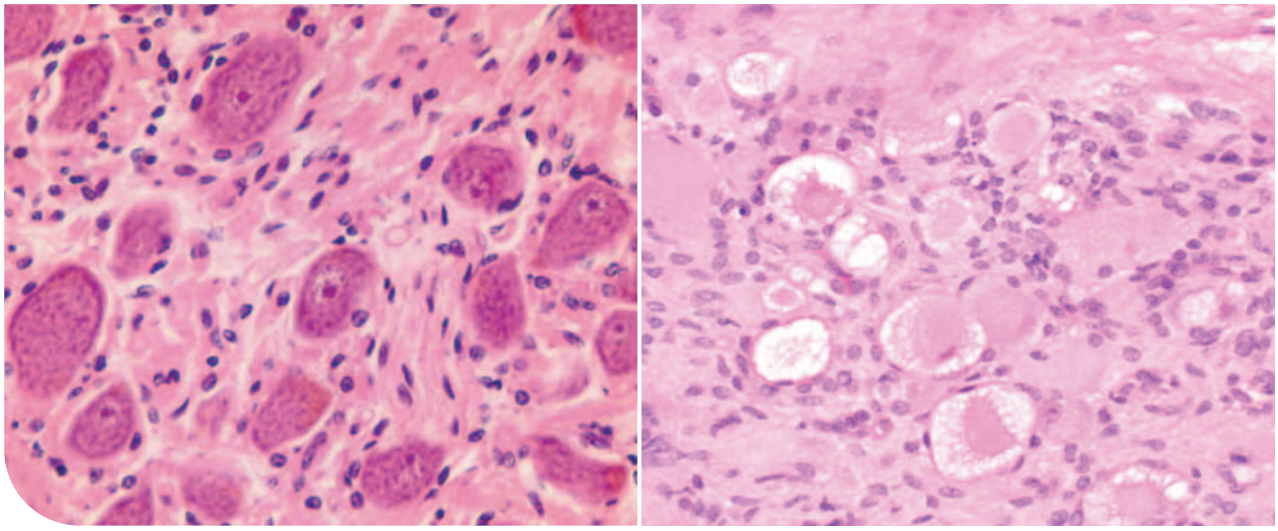


Photo: Professor Elspeth Milne

Fig 1 (left). Normal ganglion with abundant purple granules in the cytoplasm and a pale, round nucleus. (Right). Ganglion from a case of EGS showing degenerative changes including cell swelling and loss of cytoplasmic granulation and nuclei.

Later studies showed that a proportion of horses that died of Grass Sickness did have histo-pathological changes in neurones (cells of the nervous system) in ganglia (nerve clumps/junctions) in the autonomic nervous system (see Fig.1). Moredun scientists provided evidence that the neurotoxic effect could be transmitted from the liquid portion of blood (serum or plasma) from infected ponies to normal asymptomatic ponies ([7]Gilmour and Mould, 1977).

Many organisations and individuals, including substantial legacy benefits over the years, have contributed to the Equine Grass Sickness Fund. These funds have supported numerous studies conducted by scientists at the Royal (Dick) Veterinary School amongst others. Recently, there has been substantial progress in the field of both, *post-* and *ante-mortem* diagnostics, providing hope of the development of a minimally invasive diagnostic test for the disease in the future. Despite advances in specialised nursing and syndrome management improving the outlook of horses affected by the chronic form of the disease, the cause of Grass Sickness is yet to be confirmed, but it is now thought to be of multifactorial origin.
In 2021, Moredun appointed a Fellow to undertake a review of the research, to establish a biobank of blood and tissue samples from Grass Sickness cases, and to plan ways forward to continue to research on this very damaging disease.

I would like to thank Drs Tom McNeilly, Adam Hayward, Kim Thompson, Mara Rocchi and Kathy Geyer for help in developing this story.

References:

1. Froy, H., Sparks, A.M., Watt, K., Sinclair, R., Bach, F., Pilkington, J.G., Pemberton, J.M., McNeilly, T.N., Nussey, D.H. (2019). Senescence in immunity against helminth parasites predicts adult mortality in a wild mammal. Science 365(6459):1296-1298. https://doi.org/10.1126/science.aaw5822
2. Hayward, A.D., Pilkington, J.G., Wilson, K., McNeilly, T.N., Watt, K.A. (2019). Reproductive effort influences intra-seasonal variation in parasite-specific antibody responses in wild Soay sheep. Functional Ecology 33(7):1307-1320. https://doi.org/10.1111/1365-2435.13330
3. Duff, P., Fenemore, C., Holmes, P., Hopkins, B., Jones, J., He, M., Everest, D., Rocchi, M. (2020). Rabbit haemorrhagic disease: A re-emerging threat to lagomorphs. Vet Record 187(3): 106-107 https://doi.org/10.1136/vr.m3131
4. Costa, J.Z., del Pozo, J., McLean, K., Inglis, N., Sourd, P., Bordeianu, A., Thompson, K.D. (2021). Proteomic characterization of serum proteins from Atlantic salmon (*Salmo salar* L.) from an outbreak with cardiomyopathy syndrome. Journal of Fish Diseases 00: 1-13. https://doi.org/10.1111/jfd.13488
5. Kitiyodom, S., Trullas, C., Rodkhum, C., Thompson, K.D., Katagiri, T., Temisak, S., Namdee, K., Yata, T., Pirarat, N. (2021). Modulation of the mucosal immune response of red tilapia (*Oreochromis* sp.) against columnaris disease using a biomimetic-mucoadhesive nanovaccine. Fish and Shellfish Immunology 112:81-91. https://doi.org/10.1016/j.fsi.2021.02.017
6. Holman, H.H., Gordon, W.S., Pattison, I.H. (1944). Observations on the pathology and histology of grass sickness in horses. Journal of Comparative Pathology 54: 97-107.
7. Gilmour, J.S., Mould, D.L. (1977). Experimental studies of neurotoxic activity in blood fractions from acute cases of grass sickness. Research Veterinary Science 22(1): 1-4. https://www.ncbi.nlm.nih.gov/pubmed/841191

The thoughts of Lee Innes, Director of Communications

During this time of the Covid pandemic, which has literally stopped the world in its tracks, people are more aware than ever of the power of science and knowledge to solve problems and tackle some of the biggest challenges we all face. Infectious diseases, in particular zoonoses, remain a significant challenge requiring a One Health approach to bring together people with different expertise to develop effective solutions.

When Moredun was set up over 100 years ago, the founders recognized the importance of conducting research to tackle infectious diseases of livestock and to make sure that new knowledge was communicated effectively to those who would benefit from it. They identified the problem, worked collaboratively to take action and through hard work, focus and persistence achieved remarkable success.

The world in 2021 is a very different place from 1920, but the research being conducted at Moredun is still highly relevant to help solve major challenges such as, combatting infectious diseases, safeguarding food security, improving the sustainability of livestock farming while helping to protect biodiversity and our natural resources. This is where a One Health holistic approach to prevention and control of infectious diseases is so important to help protect the health of people, animals, wildlife and our environment.

Photo: www.shutterstock.com

Moredun's ethos is that disease prevention is better than cure so much of the research effort has involved understanding the causes of disease; immunological resilience and resistance to pathogens, transmission of pathogens in animals, people and the environment and using this knowledge in collaboration with others to develop effective disease control strategies. Moredun's outstanding success in vaccine development, recently to combat parasitic worms, has provided much needed new tools to tackle livestock disease across the world, supporting green farming techniques to reduce reliance on the use of drugs and pesticides and to increase the efficiency of livestock production and reduce their environmental impact.

An understanding of zoonotic pathogens and the risks they pose to people, animals and the environment has enabled Moredun scientists to work with others across different sectors taking a One Health approach to develop effective intervention strategies to help prevent disease and to protect the quality and safety of our food and water. With our changing climate, agricultural and land management practices, there are also new disease challenges emerging and the work of Moredun scientists on horizon scanning and disease surveillance is vital to highlight new areas for research and to develop the required diagnostic tools and tests.

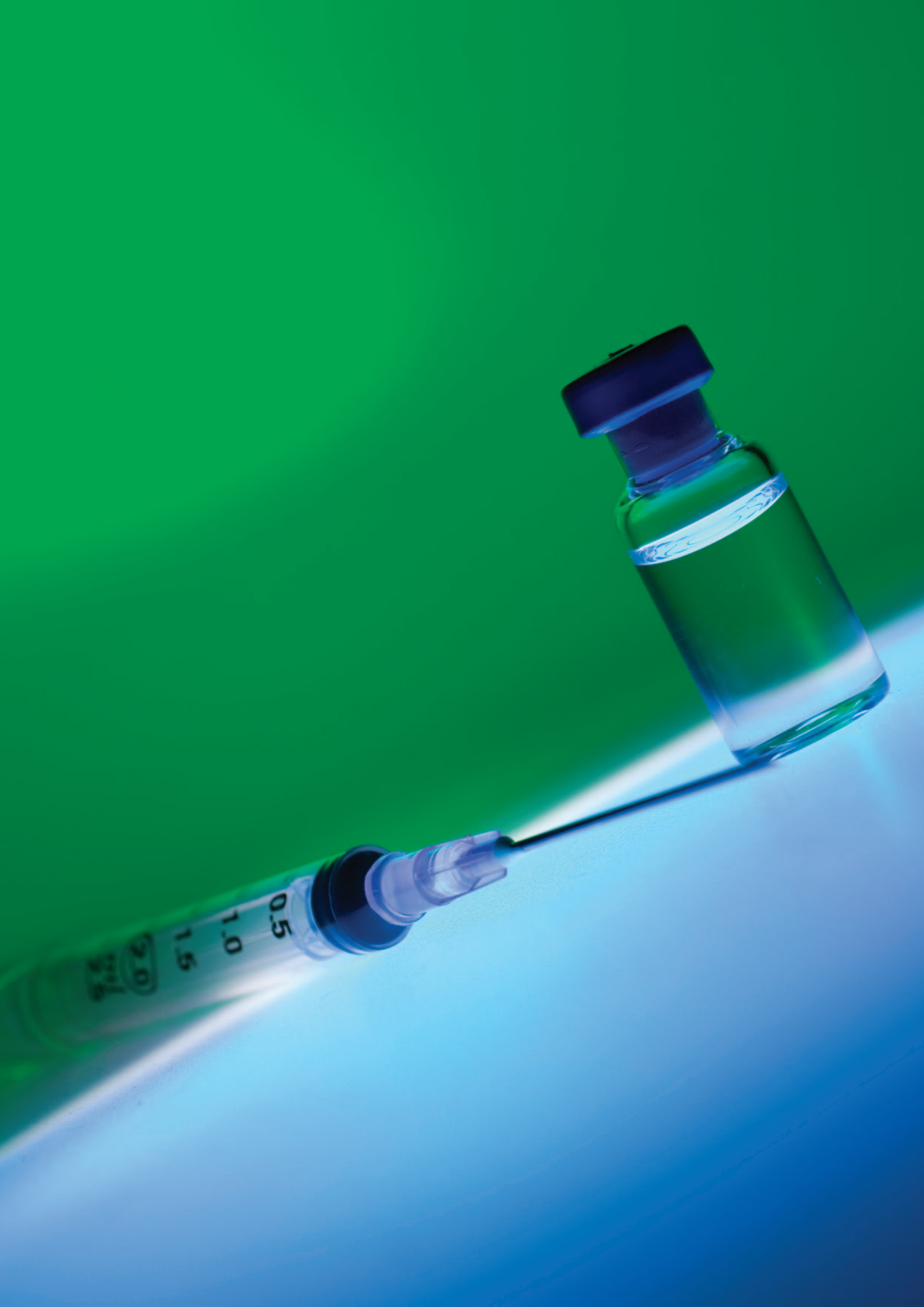
Photo: www.shutterstock.com

The focus on developing solutions to combat infectious diseases has enabled Moredun to build up a highly skilled workforce and laboratory infra-structure to enable research into high risk pathogens. These resources were used very effectively to help in the national effort to tackle the Covid 19 pandemic when Moredun staff, together with SRUC, worked with colleagues in the NHS to provide extra capacity for PCR testing for SARS-Cov-2 virus, helping NHS hospitals and care homes across Scotland. This was a great example of One Health in action and Moredun and SRUC together were the first national veterinary facility to step up to help the NHS and the government during the pandemic and showed the benefits of a collaborative One Health approach.

It would be very interesting to have a conversation with some of the early pioneers of Moredun to see what they would think of how the organisation has developed and grown over the years into the world renowned Research Institute it is today and still owned and governed by farmers. I hope they would be proud of what they set up over 100 years ago and for all that has been achieved to find out the causes of many diseases, the development of specific, sensitive and rapid diagnostic tests, novel vaccines, new treatments and management strategies to prevent and control disease and the new opportunities for One Health approaches. Moredun has a long and proud history of education and training of postgraduate students coming from many different countries across the world and now has an international workforce.

The unique relationship between the scientists and livestock farmers at Moredun has been the key to driving innovation and ensuring that the science and technology developed is aimed at practical outputs that can be used to make a positive impact to the health and well being of animals, people and our natural environment. I have been very fortunate to have spent the majority of my research career at Moredun and I have greatly enjoyed the opportunity of working together with, and learning from, farmers, veterinarians and many others in the livestock and land based industries to help develop solutions to tackle disease. As part of Moredun's Centenary celebrations we have been recruiting new Moredun Research Fellows aimed at talented early career researchers to progress work in new areas and to expand our collaborations with the farming industry through the fantastic connections we have with our UK wide Moredun Regional Advisors.

We have a lot to thank the farmers for that founded Moredun back in the 1920's, for their foresight in setting up an organisation linking those conducting the research with those that need and use it and this model is as relevant today as it was then. Moredun has a very exciting future ahead and we greatly appreciate the advice from farmers, vets and others working in the livestock industry on our Boards and we would like to thank all of our Moredun Foundation members for their invaluable support.


0.5
1.0
1.5

Produced by
The Moredun Foundation
Pentlands Science Park, Bush Loan, Penicuik, EH26 0PZ, Scotland

Phone: **+44 (0)131 445 5111**
Fax: **+44 (0)131 445 6235**
E-mail: **info@moredun. org. uk**
Website: **www.moredun.org.uk**

Photo: www.pixabay.com