Dr Rebecca Drummond, Academy grant awardee working on fungal brain infections

Animals in research

Why our researchers work with animals and our work to minimise their use

The Academy of Medical Sciences

Why we use animals

The Academy of Medical Sciences is committed to the appropriate use of animals in research and openness around the animal research we fund.

Our position on animals in research

We fund high quality research to improve health and wellbeing for people in the UK and around the world. Our grant schemes fund medical research to better understand disease, from cells grown in a laboratory, to tissue samples, computer models and, where appropriate, animals.

We consider the use of animals to be essential in biomedical and health research to understand the living body and what goes wrong in disease, and so develop safe and effective methods of prevention and treatment.

We do not take the decision to support and fund animal research lightly.

- **We use expert peer review** to ensure we fund only high-quality research where the benefits to human and animal health outweigh harms to animals.
- **We only support research using animals when there is no alternative** to find out the same information without using animals.
- **High standards of animal welfare are critical** as this both minimises pain and discomfort for the animals involved and also enables reliable research.
- **We only fund research that complies with the law**; all work is carried out in line with strict Home Office guidelines.
- **We support the principle of the 3Rs to refine, reduce and replace the use of animals in research.**

Our full position statement on the use of animals in the research we fund, yearly statistics on animals in our research and more can be found on our website.

We are committed to openness around the use of animals in research we fund. Read on to find out how our grant awardees and programme participants use animals to help patients, and how they are refining, reducing and replacing the use of animals.

www.acmedsci.ac.uk/animals

Using mice to treat cancer

Dr Shoba Amarnath, Academy Springboard grant awardee at Newcastle University (2017-2021)

What is the aim of your research?

Our laboratory is interested in how our immune system is controlled and regulated, specifically within the context of cancer. We are particularly interested in the early adjustments and changes to our immune system when tumours begin to develop. By understanding these important early checkpoints, we will be in a better position to activate and enhance our body's own immune response against cancers.

Why do you use mice?

The immune system of a mouse is very similar to humans and mice are a fantastic model system to understand regulatory checkpoints of the immune system.

We use mice to understand the role of specific genes in controlling the immune system. New scientific advances allow us to add and remove genes from mice, with their short life cycle enabling us to rapidly understand what effect this has.

We simply cannot understand early checkpoints in tumour immune suppression in patient tissue samples alone: we need to understand the immune system within the context of other living organs in the body.

Mice are indispensable in this type of cancer research.

"Some of the immunotherapies known as checkpoint inhibitors that are currently being used to treat metastatic cancers were first developed in the mouse models of cancer we use in our laboratory."

How have you refined the use of animals in your work?

We work very closely with the animal technicians in our centre to refine our research practice. We consult trained animal experts on the best approach to mouse colony management and breeding protocols, which improved how we care for our mouse colony to include reusable enrichments such as mouse tents and mouse igloos.

Furthermore, since we are interested in early events that alter the immune response in cancer, our animal models have a very low tumour burden throughout our experiments. We humanely kill each mouse at very early stages of their cancer development, minimising the amount of pain and distress involved.

Using mice to study fungi

Dr Rebecca Drummond, Academy Springboard grant awardee at the University of Birmingham (2018-present) and women in science programme participant

What is the aim of your research?

Fungal infections are a serious problem around the world, causing life-threatening illness in vulnerable patients, such as those with cancer, COVID-19 or AIDS. In fact, more people die worldwide from fungal infections each year (~1.5 million) than breast cancer or malaria. I try to understand how our immune system responds to fungal infections to develop better treatments and identify patients who are most at risk.

We focus on fungal infections of the brain that are often deadly, killing 10-15% of all patients with HIV living in low- or middle-income countries (~80-100,000 deaths each year). The brain has its own specialised immune cells, called microglia, which act as lookouts for damage or infection in the brain. We study how these microglia cells sense and respond to fungi.

Why do you need to use animals?

We aim to understand which parts of the immune system protect against fungal infection. This can't be done with computational methods or cells in a dish.

The microglia cells we work on stop functioning when removed from the brain and can't be donated by healthy volunteers. We also can't rely on patients, since they typically arrive at the clinic too late for us to study early disease stages and are often also suffering from underlying health disorders or another infection, meaning we can't assess exactly what the immune system is responding to. Unfortunately we must therefore ultimately use mice to analyse the anti-fungal immune response in a controlled whole-body system.

In addition, with mice we are able to add or delete genes, meaning that we can directly find out which genes are protecting us against dangerous fungal infections. We discovered why a gene called CARD9 is so important: human patients with a mutation in this gene spontaneously develop fungal brain infections. By studying mice with a CARD9 mutation, we were able to show that the microglial cells in the brain depend on that gene to remove the fungus.

"Our discovery has enabled us to work with other doctors and scientists to rule out ineffective treatments."

For example we now know bone marrow transplants won't work for replacing cells damaged by fungal infections, as microglia aren't replaced by bone marrow.

How have you refined the use of animals in your work?

Working with mice in research is ethically challenging. We ensure we use the most refined methods when caring for our mice. This includes carefully designing our infection studies to expose the mice to the minimum required amount of fungus and closely monitoring animals for signs of progressing infection. This is done with the support of our animal facility staff who are experts in mouse behaviour and care.

We also carefully design our experiments to use the minimum number of animals possible to get statistically robust data, and also try to collect as much data as possible from every mouse. This makes for some very busy days in the lab, but means we not only reduce the number of animals required overall, but we also obtain much better data as we can correlate our findings within the same animal.

Using rats to treat pain

Dr Kirsty Bannister, Academy Springboard grant awardee at King's College London (2018-present)

What is your research focus?

I am interested in understanding how the central nervous system regulates pain.

When short-lived, pain is advantageous: the pain of a broken ankle ensures that we don't put too much weight on it before the bone is healed. However sometimes pain persists even after an injury has healed. This type of pain has outlived its biological purpose and is called chronic pain, and diseases involving this are devastating: they severely impact the quality of life of up to two thirds of affected individuals.

By investigating central nervous system mechanisms behind the sensation of pain, I hope to help solve the lack of effective treatments for patients with chronic pain.

Why do you use animals?

My research uses healthy rats and mice as well as animal models of pain caused by nervous system damage and bone cancer. The use of rats in my studies and modelling their different pain states is critically important.

This work cannot be modelled in cell culture systems or explored in humans in a comparable manner. The neuroanatomy and physiology of the rats we use is well understood, and they have comparable central nervous system complexity to the human. This means in rodents we can unequivocally establish which pathways underlie pain processing and which brain areas they are influenced by.

"My research has revealed that the central mechanisms that drive pain in the early stage of cancer-induced bone pain are different to those that underpin pain the late stage of the disease."

This will change how we use pain-relieving therapies in future for cancer patients, because we have proved it can't be 'one size fits all' throughout the disease trajectory.

Tell us about your work to improve animal welfare?

While conducting research in animal models of pain it became clear that the process of administering pain relief could be refined. Global standard practice is to administer no or limited pain-relief medication to animals during surgeries to induce a chronic pain state. So I went for and won a grant from the National Centre for the Replacement, Refinement and Reduction of Animals in Research. I am demonstrating the neuropharmacological outcomes that we scientists seek to measure in animal models of chronic pain are not impacted by appropriate pain relief in the acute post-operative period.

I presented my research at two RSPCA meetings, receiving support from the RSPCA's Senior Scientific Officer as well as the Named Animal Care & Welfare Officers at King's College London and Queen Mary University. While this research is still in its infancy, we have already shared our preliminary data to all labs that model pain states in animals in our research unit. This is vital if we are going to ensure maximum uptake of refined approaches that ensure minimal animal suffering and improved animal welfare in this type of research.

Dr Kirsty Bannister, Academy grant awardee working on chronic pain from nerve system damage & bone cancer

Using zebrafish for stroke

Dr Paul Kasher, Academy Springboard grant awardee at the University of Manchester (2017-2021)

What do you work on?

My group is interested in defects in the blood vessels of the brain, such as stroke. These types of diseases are extremely dangerous for patients, and we still don't fully understand the biology behind them.

However, we do know that shortly after a stroke, there is an immune response in the brain which is thought to worsen the brain injury, and in my lab we think this inflammation might be a good target for medicines to try and reduce brain damage.

What animals do you use and why?

Rodents are the most commonly used model species for stroke research, but my lab uses zebrafish in our research – in particular zebrafish embryos and larvae up to five days post-fertilisation.

Our development of zebrafish larvae as a new alternative model for stroke research is replacing and reducing the number of mammals required for this research, aligning directly with the principles of the 3Rs. We have shown that some of the classic consequences of bleeding in the brain in zebrafish larvae are remarkably similar to that seen in stroke patients.

Zebrafish are excellent replacements for mammals in stroke research for many reasons:

- They have significant genetic resemblance to humans, allowing us to model human disease.
- Unlike most rodent models which require surgery, bleeding in the brain in zebrafish larvae occurs spontaneously, which aligns more closely to what happens in patients.
- Zebrafish breed easily and develop quickly, making it easy to obtain sufficient sample sizes for drug testing.
- Zebrafish are translucent, meaning we can use simple microscopes to observe internal organs such as the brain. If we use zebrafish which have been genetically modified to express fluorescently labelled proteins in different cells, we can even use powerful microscopes to track brain cells in living animals.
- Zebrafish recover from brain haemorrhage and brain injury incredibly quickly, and we hope that understanding this recovery process is something we could apply to the human brain.

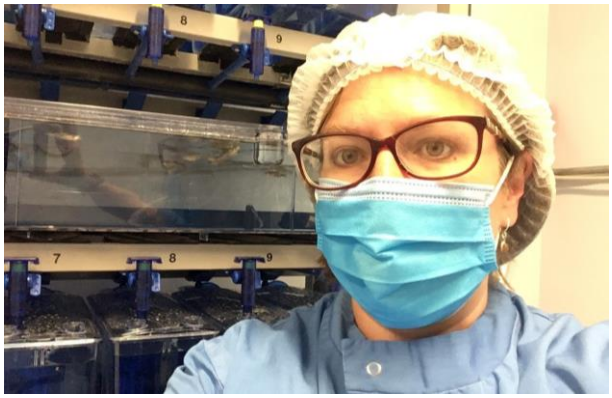
What have you been able to find?

We have used zebrafish to screen for drugs that can reduce brain cell death after bleeding in the brain. We have screened a library of 2000 drugs – this scale of drug testing has not been possible before using rodent models.

The aim of this research is to accelerate the drug development pipeline for patients. The hope is that we can identify drugs that can be 'repurposed' for stroke and tested in humans more quickly. We have identified some interesting candidate drugs already – one class with significant implications for translation to humans, which is under review for publication – watch this space!!

Using zebrafish for oedema

Dr Alice Pollitt, Academy Springboard grant awardee at the University of Reading (2016-2020)



What is the aim of your research?

In my lab we work to understand how our blood platelets communicate with other cells in our bodies.

When you have a cut, it is your platelets that stick together to form the clot that stops further bleeding and starts the healing process. However, if a clot occurs inside our bodies, it can be very serious and result in a heart attack or stroke. Platelets perform lots of other functions, such as being part of our body's system to fight infection and maintaining separation between our lymphatic and blood systems. Any disruption to how platelets work can have devastating effects on our health.

What have you discovered?

"One area of my work, funded through a Springboard grant from the Academy, is for the first time revealing the role of platelets in maintaining the correct function of the lymphatic system, our body's network of waterways."

Less well known than our cardiovascular blood system, these tubes transport excess fluid away from our soft tissue and into the thoracic duct, where it is returned into the bloodstream. If the ability of the lymphatic system to function is disrupted, then fluid builds up under the skin leading to swelling, known as oedema.

Oedema is a debilitating and life changing condition and, despite over a quarter of a million people living with the condition in the UK, there are currently very few ways to treat it.

We are finding that some of the new drug treatments being developed for autoimmune diseases and cancers risk interfering with how platelets maintain the separation of the blood and lymphatic vessels, potentially triggering oedema.

Why are animals used in your research?

84% of genes linked to a human disease have an equivalent in zebrafish: we use zebrafish to understand the communication and regulation between platelets and the cells lining the lymphatic system. Zebrafish enable us to understand these genes, and so identify possible serious side effects of emerging therapies. This sort of cross-cell interaction can't be replicated in a test tube.

How are you working replace, refine or reduce the use of animals in your work?

Our work is done by generating modified platelets in animal models. However, because platelets have no nucleus, there are currently no reliable methods to modify donated human platelets.

We've won funding from the National Centre for the Replacement, Refinement and Reduction of Animals in Research to enable this by delivering modifying compounds into donated human platelets. Hopefully this will enable researchers in the future to use donated human platelets for this type of research, replacing the animal models currently used.

The Academy also supports researchers working solely on models that replace animals in research completely.

Using computer models for testing new drugs

Dr Dennis Wang, Associate Professor in Genomic Medicine and Machine Learning at the University of Sheffield and Academy Springboard grant awardee (2018-present)

I started out in computer science, then did a PhD in biostatistics and worked at medical research agencies and hospital genomics labs. Then I moved into industry, joining AstraZeneca's drug development team and collaborating with Microsoft Research. Now I'm back fully embedded in academia as an Associate Professor at the University of Sheffield.

My team uses machine learning algorithms and statistical models to integrate data across genomics and patient records. This machine learning can connect patients based on commonalities, link different diseases together and ultimately predict disease outcomes.

Some of our work so far has identified predictors of survival and treatment response for people with non-small cell lung cancer, discovered immune system changes that connect heart disease, lung cancer and dementia. We have also developed computer models of kinase signalling pathways that researchers can run to test how drugs work and so potentially save many animals and patients from being tested with ineffective drugs.

Dr Dennis Wang presenting his research at an Academy event

And more, we consider human, animal and environmental health as a single interconnected system. Discover the researchers we support via this 'one health' approach.

Preventing rabies for both dogs and people

Professor Richard Mellanby, Professor of Comparative Medicine at the University of Edinburgh and member of the Academy FLIER leadership programme (2019-2021)

I'm really glad that the Academy is including vets in the FLIER leadership programme. There is a great deal of commonality between human and animal health, so it's a two-way street. There is also great potential for developing better animal models for medical research, which could mean we use fewer experimental animals in the future.

I'm interested in rabies, which kills 60,000 people each year. 99% of human rabies deaths are caused by bites from infected dogs. So rabies is completely preventable through mass dog vaccination.

I research how to deliver more effective vaccination campaigns in low resource settings. In Malawi, we redeveloped a vaccination programme to reduce staff and scale up from 35,000 dog vaccinations in 20 days to 30,000 dog vaccinations in just 11 days.

The COVID-19 pandemic has highlighted the importance of considering animal reservoirs of human pathogens. I hope one consequence of the pandemic is a renewed interest in controlling zoonotic diseases for both human and animal health. As our work with rabies shows, this does not require major scientific breakthroughs. It simply requires cost-effective implementation of established disease prevention strategies on a global scale, and funding for research on how to implement this pre-existing knowledge.

Preventing cattle lameness

Professor George Oikonomou, Professor of Cattle Health and Welfare, University of Liverpool and Academy Starter Grant awardee (2016-2020)

The preliminary data from my Academy Starter Grant allowed Us to win a big BBSRC grant, which has allowed us to complete the most comprehensive cattle lameness study in the world.

Farmers want to use Holstein Friesians because they're high-producing for milk, but selective breeding has made this breed more susceptible to lameness. 3 out of 10 cows may be lame at any point. When we work closely with a farm, we can get this down to less than 1 in 10.

Our cattle genetics research could still generate findings that could be applied in the human world. It's not always easy to bring these worlds together and we are missing out on opportunities. Ultimately, our research on cattle lameness could improve food security, sustainability, and animal welfare all over the world.

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