Imperial College London

ANIMAL RESEARCH

Annual Report 2015/16

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FOREWORD

Animal research at Imperial

Imperial College London's first Animal Research Annual Report was a public statement of institutional and cultural change at the College, focusing on the implementation of our Action Plan for world class animal research.

This second edition moves on from this to highlight the outcome of some of our work involving animals. In this report you can read interesting case studies that highlight the transformative impact our work involving animals is having in a number of areas of scientific research. The fact that we are now in a position to focus on the outputs and impact of our work – rather than the systems and structures that underpin it – shows how far we have come in such a short time in embedding the Action Plan in our 'business as usual'. We now have the structure in place to focus on what we do best: excellent science.

Looking back over the past year, a very significant development was the appointment of Professor Marina Botto as Director of Bioservices, the last position recommended by the Action Plan to be filled. Professor Botto was the outstanding candidate for this position, which is responsible for overseeing animal care and our animal research strategy at the College. She is a senior professor in the Department of Medicine who commands the respect of the academic community, and whose considerable experience of animal research makes her well-placed to engage with the staff who make this work possible. Although in post for less than a year, her impact has already been profound. Professor Botto reflects on her role on page 2.

Professor Botto's appointment has allowed us to move ahead with a strategic review of our animal facilities. It has been clear for some time that some of our facilities do require modernisation, and over the coming years we will be investing significant resources to ensure that the standard and size of our facilities are appropriate for the future needs of our animal research community.

One development I was particularly pleased about this year is the outcome of an audit into our internal processes and policies in relation to animal research. With the governance structure set out in the Action Plan in place, we felt it was timely to seek an independent assessment of the changes we have made. As such I asked our internal auditors, KPMG, to review the implementation of the College's Action Plan, which was based on the recommendations of the Brown Review, and ongoing monitoring arrangements. The result was very positive, with the audit finding "significant assurance with minor improvement opportunities". Having witnessed at first-hand how hard a number of colleagues have worked over the past couple of years, this independent verification was greatly reassuring that it has all been worthwhile and that we have a robust structure in place.

Another important development was the extension of Imperial's animal research policy to cover work not regulated under the Animals (Scientific Procedures) Act. This means, for example, that staff carrying out animal research outside the UK must now register this activity and, if appropriate, submit the proposed work to the College's Animal Welfare and Ethical Review Body (AWERB) for approval. I would like to thank Professor Maggie Dallman, who chairs Central AWERB, for guiding this initiative through and the animal research community for the positive way that they have engaged with the new policy. You can read more about it on page 17.

All this positive work does not mean we can be complacent, however. We rightly set very high standards for ourselves. I expect Imperial to be excellent in all that we do, and maintaining these high standards requires commitment, hard work and vigilance from all of us. It is also important that we recognise and reward excellence, and so I would like to extend my sincere personal congratulations to the winners of the Provost's Awards for Excellence in Animal Research. You can read about their achievements on page 22.

Finally, an active engagement in the 3Rs – the replacement, reduction and refinement of animal experiments – continues to have a highly beneficial effect at Imperial, particularly in making people think very carefully about the number of animals that they use in their research. We continue to see some innovative and notable applications of the 3Rs around the College, much of it a result of the tireless work of Professor Richard Reynolds, to whom I am grateful for his ongoing commitment to this important subject.

I hope that you enjoy our Annual Report, and I look forward to continuing on this upward trajectory in the next year.

Professor James Stirling

Provost and Establishment
Licence Holder
August 2016

LEADER

Strategic leadership of animal research

Professor Marina Botto is Imperial's first Director of Bioservices, a position created under the College's Action Plan for Animal Research.

"My role is the strategic leadership of animal research," she says, "and making sure we continue on the path of improving our culture and implementing the changes to which we are committed."

She adds this new position to her roles as Professor of Rheumatology and Director of the Centre for Complement and Inflammation Research. Both a clinician and a scientist, her research focuses on an autoimmune condition called systemic lupus erythematosus, and includes work with mice to understand how the disease develops.

"I've been working with animals in research for more than 15 years, my academic career is underpinned by this work. In taking on this role, I have the opportunity to give something back to the animal research community and I am fully committed to do so. Being an academic, I know how important it is to create the right environment for the welfare of the animals and the research."

Throughout her career at Imperial, Professor Botto has been actively involved in the governance of animal research, contributing to committees and championing the Action Plan. Becoming Director of Bioservices felt like a natural development, she says. "I know the history, I know how we got here and where we want to go."

Her appointment in July 2015 completed the new governance structure for animal research at Imperial. "My role now is to build on what we've already achieved, to embed the ideas set out in the Action Plan into working practice and continue to promote the cultural improvement programme."

This means actively pursuing the 3Rs (replacement, reduction and refinement), encouraging communication about animal research and fostering a sense of community among the people involved, at all levels.

"You will not improve the culture simply by creating a new structure," she explains. "Improvement in culture comes from openness in animal research, of not being afraid to talk about it, and from creating a much more harmonious interaction between researchers and staff, so that everyone feels that they are working together. This is already happening,but we want to go further."

This sense of community is something she relies on in her new role. "It's never the job of a single person, and I'd like to express my gratitude, both to the Central Biomedical Services (CBS) staff and to my academic colleagues who are contributing to the various CBS committees. Without their time and commitment, these committees

wouldn't work and we would not be able to implement our Action Plan."

Meanwhile, interactions with the public are already improving. "With the help and encouragement of our communications staff, we have already been more open in digital and face-to-face communications," she says. "If we achieve high standards in animal research, then my colleagues can be open with the public about their work."

For the future, Professor Botto is developing a long-term strategy for animal research at Imperial. "This will ensure that our facilities remain of a very high standard and fit for purpose," she says. "I want to make sure we continue to provide facilities that have high standards of welfare for our animals and can deliver the best science for our researchers. These will be the indicators of success."

"In taking on this role, I have the opportunity to give something back to the animal research community and I am fully committed to do so."

DISCOVERIES

Recent findings from animal research

Imperial research involving animals is improving our ability to develop new medical treatments and tackle major diseases, from Parkinson's disease to cancer.

Nerve study gives hope for treatment of spinal cord injury

The nerves in the spinal cord have a very limited ability to regrow. If they are damaged it is often permanent and there are currently no effective treatments.

Now scientists have identified a series of proteins that seem to restrict nerve growth. They treated mice with spinal cord injuries with drugs called nutlins, which stop these proteins interacting. They found they were able to make nerves regrow, first in mice with injuries to the optic nerve and then in mice with spinal cord injuries.

Mice treated with a placebo made only a slight recovery in their movement ability after a spinal cord injury. Mice treated with nutlins made a much stronger recovery, achieving higher scores on tests assessing their movement.

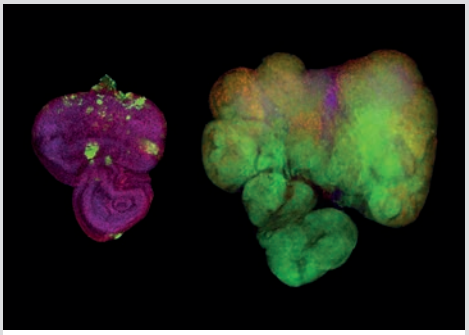
Sparrows with unfaithful 'wives' care less for their young

A new study shows that male sparrows can judge if a spouse is prone to infidelity, providing less food for their brood if their partner is unfaithful.

Sparrows form pair bonds that are normally monogamous, but many females are unfaithful to their partner and have offspring with other males.

An Imperial researcher followed the entire sparrow population of the island of Lundy in the Bristol Channel for 12 years. She genotyped every sparrow, allowing them to build up precise family trees and find out which females were most unfaithful.

The research showed that males make the decision of how much to provide for their chicks based on the tendency of their partner to cheat.

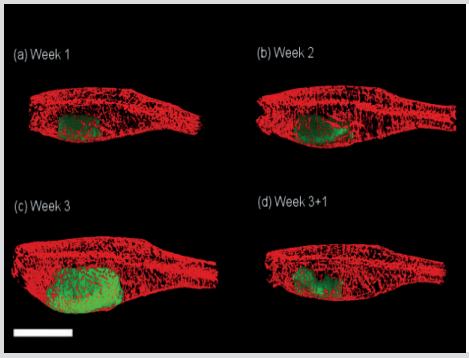


Sugar switch may explain link between obesity and cancer

Researchers working with fruit flies have identified a mechanism that allows cancer cells to grow rapidly when levels of sugar in the blood rise.

They studied tumours in flies fed on high sugar diets and compared these to flies fed a normal diet. They found that flies that were fed a normal diet grew small, benign tumours (left) but flies that were fed a high sugar diet developed large, malignant tumours (right).They found that a protein called salt-inducible kinase acts like a sugar sensor. In response to raised glucose levels it switches on a particular growth pathway, which allows tumour cells to thrive.

The study may help to explain why people who develop conditions in which they have chronically high sugar levels in their blood, such as obesity, also have an increased risk of developing certain types of cancer.



Tracking cancer progression without surgery

Scientists at Imperial and University College London have adapted a method called optical projection tomography to image and measure tumours and the blood vessels that support their growth.

They used the method to create 3-D images of cancer developing in a live zebrafish.

Since the same organism can be studied over time, the method could reduce the number of animals used in research.

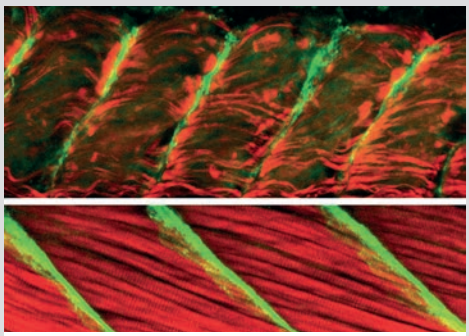
The approach uses genetic fluorescence labelling techniques, which allow internal organs to be highlighted in different colours. The researchers studied the zebrafish at different points over time allowing them to observe the development of blood vessels as tumour size increased.

Study shows how the brain can trigger a deep sleep

Scientists have discovered that chemically switching on one area of the brain, the preoptic hypothalamus, can trigger a deep sleep.

The researchers used a genetic tagging system to mark neurons in mice that were activated both during sedation and in deep sleep. When they subsequently targeted those neurons with a chemical, it was sufficient to produce a deep sleep in the mice.

The knowledge that one distinct area of the brain triggers this kind of deep sleep paves the way for the development of better sedative drugs and sleeping pills.



Clue to heart disorder found in fish's tail

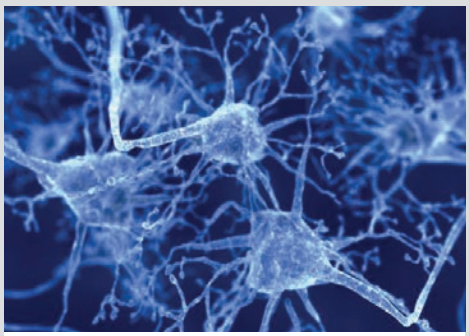
By studying muscles in zebrafish tails, researchers have found that a gene called Popeye domain containing-1 seems to have a role in heart disorders. As its name suggests, the gene has a role in 'gluing' muscle cells together. When the gene is mutated, the muscle tissue becomes significantly weakened and damaged.

This image from the study shows the muscles in the tail of a zebrafish with a mutated version of the gene, leading to damage in the tissue and, below it, a zebrafish tail with a normal copy of the gene.

Scientists solve the mystery of earthworm digestion

Earthworms play a key role in ecosystems because they can digest fallen leaves. These leaves contain toxic chemicals, produced by plants to deter plant-eating animals, but worms are able to overcome the problem.

Scientists studied worms using modern visualisation techniques based on mass spectrometry – or MALDI imaging. They found a group of molecules called drilodefensins that were concentrated in the worms' guts. These molecules counteract plant toxins, allowing worms to digest fallen leaves.



New technique targets source of Parkinson's disease

Researchers at Imperial are targeting the brain affected by Parkinson's disease.

They worked with rats that had been treated to recreate the disease symptoms and used a harmless virus to deliver a genetic 'switch' to the target neurons. The rats were then given a drug that was designed to activate the 'switch' and stimulate the neurons.

Following the treatment, the rats made an almost complete recovery. The researchers hope it will be possible to transfer this technique into patients in the next five to ten years to help them regain mobility.

FOCUS

Tackling infection and protecting biodiversity

This page: Professor Matthew Fisher, left, with a PhD student from his Lab.

Professor Matthew Fisher, Professor of Fungal Disease Epidemiology at Imperial, is conducting research with amphibians that is helping to protect diverse species from infection by the world's most deadly fungus.

In 2002, a rather odd scientific correspondence was taking place between two young researchers. Every few weeks Matthew Fisher at London Zoo would receive a package from Dr Jaime Bosch in Spain containing piles of decomposing amphibians.

Dr Bosch was studying the calls of the midwife toad in the mountains north of Madrid and had been horrified to see thousands of the animals wiped out by an unknown disease. Matthew Fisher, now a professor in the Department of Infectious Disease Epidemiology at Imperial, thought he knew what the disease might be, but he needed a live sample to work with.

"Eventually he managed to get a reasonably fresh one to me," Professor Fisher recalls, "and it was one of those eureka moments. I was looking through the microscope and saw the motile, very zippy zoospores of *Batrachochytrium* in the culture. At that moment I knew that it was game-on."

What he could see were the asexual spores of the fungus *Batrachochytrium dendrobatidis* (*Bd* for short), which causes the disease chytridiomycosis in susceptible amphibians. Discovered in 1997, the fungus had been linked to mass deaths of amphibians in North and Central America, but never before in Europe.

"We were able to prove that this was *Batrachochytrium* and to start doing the genetics and genomics to tie this global picture together," he goes on. "I've been running with this single observation through a microscope ever since."

Even so, this is not Professor Fisher's main line of research. Now at Imperial, his principle interest is in emerging fungal diseases that affect humans, such as those associated with HIV.

"Not once in my ten years here have I had to formally justify why I'm working on a disease that has nothing to do with humans," he says. "People see the intrinsic value of the research for its ethical and moral implications: we need to work on wildlife diseases, they are incredibly important."

Bd is a very special case. The disease caused by the fungus has had the greatest impact on biodiversity of any infectious disease in the world – human or otherwise. "It has caused over 200 full species extinctions, which is not something any other infectious disease has been able to do. For that reason alone it is an extraordinary pathogen."

It has also penetrated almost every ecosystem on the planet where amphibians are found, often thanks to the international trade in these animals.

Having identified *Bd* as the cause of these amphibian deaths, attention has turned to how the fungus and its hosts interact, and why infection does not always result in the disease and death. This varies between host species and even from place to place. One reason for this is that the bacteria living on an amphibian's skin in a particular location appear to play a role in how it reacts to the fungus.

In contrast to medical research, where animal models often stand in for humans, the aim here is to be as close to nature as possible. "When we do these experiments we want to find out something about that species, in that place, and what we can do about their infection," Professor Fisher explains.

For example, in 2010 a chytrid disease appeared in the Netherlands, wiping out nearly all the country's salamanders in the following three years. Rather than *Bd*, the cause turned out to be *Batrachochytrium salamandrivorans* (*Bsal*), a related fungus previously found only in Southeast Asia.

"*Bsal* has a much more restricted host range than *Bd*. It can't infect frogs, but it's an absolutely vicious infection in salamanders and newts," Professor Fisher explains.

Britain has a large population of newts, including the protected great crested newt, so assessing the impact of a possible outbreak became a priority. To do this both the common (or smooth) newt and great crested newts from the UK were exposed to the fungus by Professor Fisher's team. The smooth newts threw off the infection easily, while the great crested newts developed very heavy infections.

"Working with great crested newts is incredibly difficult," Professor Fisher explains. "They are a conserved species in the European Union and highly protected. But if we had just used smooth newts we would have got entirely the wrong answer."

"Bsal has a much more restricted host range than Bd. It can't infect frogs, but it's an absolutely vicious infection in salamanders and newts."

Experiments using amphibians are also important in designing treatments, for instance with anti-fungal agents. Once again the most relevant results are obtained by working with the actual species infected. "These are very small experiments, very tightly defined to a specific intervention. And when we find a drug that works, we can go out and use that in nature on the animals themselves and try to clear the infection."

This was done successfully on the Spanish island of Mallorca, where *Bd* had infected colonies of midwife toads. Their ponds were drained and the surrounding areas sprayed with disinfectant. Both tadpoles and adult toads were treated with the anti-fungal agents and returned to their original ponds, once they refilled with rain water. At four out of five sites, the returned animals remained free from infection in the two following years and it is highly likely that the infection will be eradicated from the island in 2016.

While using animals caught in the wild is sometimes justified, those bred in captivity are used wherever possible. And common amphibians are used when the research questions are more general, for example looking at how the fungi function.

"A lot of our work has been done on the UK common toad, which produces incredible numbers of offspring," Professor Fisher says. "You can take some of those from the wild and be comfortable that you haven't impacted the populations."

Amphibians also have specific husbandry requirements. They take on the temperature of their surroundings, so this has to be carefully controlled in the laboratory. Tadpoles often require very clean water, and adult animals need live foods such as crickets.

Newts, meanwhile, spend their summers in water, then change their skins to live on land

over winter. This life cycle needs to be respected in the laboratory. "There is a lot to keep your eye on when you are keeping this range of species in the laboratory."

Working with protected species means that the 'reduction' aspect of the 3Rs is present from the outset. Otherwise the main strategy is to substitute non-animal experiments wherever possible. "The day-to-day running of the lab is all done with these chytrids in tissue culture, so that you don't need to go near an amphibian."

The focus of Professor Fisher's research now is to anticipate further outbreaks like the Dutch incident, where a species suddenly appears in a new context with disastrous results. "We are surveying amphibian populations around the world and using broad-spectrum approaches to discover more of these pathogens in their natural environments," he says.

For example, the protease genes present in a fungus can be read like a bar-code, giving a quick indication of its risk potential. Those fungi that seem dangerous can then be tested on other species, to prove whether or not they are pathogenic and a threat to biosecurity.

New approaches to treatment are also being investigated, for example exploiting the skin bacteria that seem to help some amphibians resist infection. Similarly there are microscopic organisms in some of these ecosystems that feed on *Bd* zoospores and could be encouraged as an alternative approach to mitigate the severity of infection.

"There are layers upon layers of microbial interactions here that we need to understand," Professor Fisher says. "Once we do, we can start to perturb these systems and hopefully push things in the amphibians' favour to reduce future losses of biodiversity."

To watch a video about Professor Fisher's research, visit: bit.ly/frogs-research

CARE

Supporting research with animals

Central Biomedical Services (CBS) provides the infrastructure and support for animal research at Imperial. Its staff are responsible for the day-to-day care of animals, and it trains both its own animal technicians and researchers new to the field in the appropriate way to work with animals.

A significant development in this training role during 2015 was the arrival of the College's first two apprentice animal technicians: Bonnie Glen and Ryan Cini. They will be spending 15 to 18 months at Imperial under a national apprenticeship scheme run with the Institute of Animal Technology (IAT).

"I studied animal care at college for two years, so I always knew that I wanted to work with animals," says Bonnie. "And when this apprenticeship came up, I applied for it straight away." Even so, she admits that what lay ahead was a mystery. "At college they talked about every other animal job apart from this one, so I didn't really know what to expect."

Ryan applied for the apprenticeship from sixth form. "I wasn't sure that I wanted to go to university, so I went for an apprenticeship instead. When I read the description of what the job was about, I thought it was pretty interesting and a bit different as well."

Bonnie and Ryan look after animals in CBS, while following an educational programme that structures the apprenticeship and prepares them for the IAT's professional qualifications. "We are set certain learning outcomes, and we have to achieve them either by doing an assignment or by showing someone how we do something," says Bonnie.

> *"I studied animal care at college for two years, so I always knew that I wanted to work with animals."*

"We are doing the same things as the junior technicians, but it is reinforced straight away," Ryan adds.

They also change facility every four months, to experience different work settings.

Halfway through their apprenticeships, both are positive about their prospects.

"You always hope that the industry you are going into will be welcoming and open, and that is exactly how it has been," says Ryan.

"I want to stick at it," says Bonnie. "I'm enjoying it."

The processes around the scheme are also a change for CBS. "There is a lot of documentation for an apprenticeship scheme, and alongside the training the apprentices have to be assessed," says Mandy Thorpe, Director of CBS (pictured right), who is very positive about the experience. "In the latter part of this year we hope to start looking for two new apprentices, so that there is some cross-over."

Staff engineer

Another addition to the CBS staff has been its first in-house engineer, Steve Steel. He has worked in the field for around 35 years, mainly for companies supplying animal facilities.

His main task is to look after CBS's automated cage-cleaning system, from daily maintenance to fixing breakdowns. "I also go to other College sites to carry out similar duties, maybe on washing equipment, or anything that the department needs repaired or serviced," he says.

Steve will also be involved in specifying and ordering new equipment, and has already turned his hand to making equipment to order.

Having an engineer on staff means more efficient service and continuity. As Steve explains, “I’m on-site all the time, so I’m easy to get hold of and I can see things through to the end.”

Outreach

During 2015, CBS also launched a series of public outreach activities, for example participating for the first time in the annual Imperial Festival. “It was quite an achievement for us to do this, because it is public-facing,” says Ms Thorpe, pictured right with colleague Wendy Steel at the event. “We talked about the animals, showed visitors the cages in which animals are housed, and invited them to do a health check on toy animals.” This initiative was expanded in 2016.

Meanwhile, school pupils were invited into the animal facilities for the first time, as part of an outreach project with Westminster Academy. Around 20 pupils visited in small groups to learn about the work of CBS. “We brought the kids into the facility, told them all about the animals, showed them around and got the technicians to talk to them,” says Ms Thorpe.

Awards

The first CBS recognition awards were also held in 2015, celebrating good practice by CBS staff and others at Imperial. And in October 2015 Ms Thorpe was awarded the Imperial College Medal, in recognition of her 40 years’ service to CBS.

Clockwise from top left: Mandy Thorpe, Director of Central Biomedical Services; Ms Thorpe and Wendy Steel, animal technologist, undertaking outreach work at the Imperial Festival; Bonnie Glen and Ryan Cini, apprentice animal technicians.

FOCUS

Complexities of the complement system

Professor Matthew Pickering's research into kidney disease involves a continual dialogue between observations in patients and work with mouse models. This helps to explain how the diseases that he studies occur, and how to develop new treatments.

His focus is the complement system, a group of proteins important in the body's defence against infection. However in some people, instead of defending the body against infection, the complement system turns on the body's own tissues. This damage appears in the kidney's filtering units, called glomeruli, so the diseases are known as complement-mediated glomerulopathies.

"I want to know how complement causes kidney injury and how to stop this from happening," Professor Pickering explains.

Genetic and in vitro studies have provided some information about why the complement proteins are abnormal in families with these conditions. However, to understand why the kidney was damaged, the research needed to use an animal model with a fully functioning immune system.

"You can't model kidney inflammation in vitro," says Professor Pickering. "To a large degree the mouse complement system is very similar to the human system, so that made modelling the kidney disease in mice a feasible approach."

To begin with, the focus of the research was a regulatory protein called complement factor H. Mutations in the genes producing this protein were associated with families suffering from C3 glomerulopathy in which another protein, C3, built up in the kidneys. Reproducing the genetic defects in mice resulted in C3 glomerulopathy in the mouse.

"We were able to get a spontaneous C3 glomerulopathy by introducing abnormalities in mouse complement factor H," Professor Pickering recalls. "That was important, because we showed causation with the genetic defect and were then able to look at how the kidneys became damaged and study ways to prevent damage from developing."

But then further patient investigations started to show additional complexities. While some families had the C3 glomerulopathy, genetic defects in factor H were also associated with a more acute illness, called atypical haemolytic uraemic syndrome (HUS). In this condition, there is blood clotting, or thrombosis, in the kidney. There is no effective treatment for atypical HUS.

"This is a dangerous disorder because if you get blockage of blood vessels in the kidney, you can't filter waste through the kidney and renal failure can occur very rapidly."

Looking closely at the way factor H operated suggested that it had two functions, one controlling levels of C3, the other protecting the lining of the kidney. Different genetic defects appeared to affect the protein in different ways, leading to the different medical conditions.

The definitive test was to try to replicate each one in mice. "We went back into the animal model, and saw these two distinct phenotypes, the thrombosis on the one hand, and the C3 glomerulopathy on the other, by changing the abnormality in the protein."

With animal models for both conditions, the next task was to look at how the kidney damage developed. For atypical HUS, Professor Pickering and his colleagues showed that it was critically dependent on the complement protein C5. "We were able to show in the animal model that if you prevent activation of C5, you don't get this disease," he explains.

Alexion Pharmaceuticals had already developed a drug for a rare blood condition that works by preventing C5 activation. When this drug, called Eculizumab, was used in atypical HUS the results were very positive. Professor Pickering says: "The drug is now licensed and approved for use in atypical HUS. C3 glomerulopathy remains challenging but many insights from the animal model have revealed potential ways to protect the kidney."

Addressing the 3Rs – the replacement, reduction and refinement of animal experiments – in this work is a natural part of conducting effective research, Professor Pickering says. "We are refining the models all the time. We are trying to make them as informative as possible and always looking at our protocols to make them efficient." Professor Pickering no longer works with the mouse model for atypical HUS. "I see this as a closed, successful story," he says. "We don't need the animal model anymore."

Meanwhile for C3 glomerulopathy, the emphasis is on choosing targets that have a clear future as therapies. "I know that it is feasible to inhibit certain steps of C3 activation in humans, so I try to model those in the mouse. If that then has an impact on disease, I know I have a solution that is translatable."

Deciding how many mice to use is a question of balance. "It's asking how we can do the experiments using the number of animals that will give us the answer we need and no more," Professor Pickering explains. "Sometimes that is not a small number of animals, because we do not want to under-power the experiments. That is just as bad as using too many animals; you just end up with uncertain data, which doesn't help anyone."

The main challenge for the future is how to approach aspects of the complement system where mice are not such a good fit with humans. For example, there are factor H-related genes which are linked to complement-mediated kidney diseases. Because these genes are very different between human and mouse, manipulating the mouse factor H-related genes would be of limited value in understanding human disease.

So Professor Pickering and his colleagues are exploring options for replacing the mouse factor H genes with those from humans, working with the Wellcome Trust Sanger Institute. "We've got data to suggest that this would be an informative approach," he says. "This relates to C3-related glomerulopathy, but it is also valuable for meningitis and age-related macular degeneration, an important eye disease. A diverse group of scientists will be interested in this new animal model and it has the potential to reveal important clues into how these diseases develop and what we can do to stop them."

FOCUS

Fruit flies signal new discoveries

Professor Irene Miguel-Aliaga and her team at the Medical Research Council (MRC) Clinical Sciences Centre are using the nervous system of the fruit fly to reveal exciting discoveries, from the link between the brain and the gut to the sexual identity of organs.

For more than a century, fruit flies – *Drosophila melanogaster* – have been used to investigate how genes control the development of single cells into complex bodies. The more recent practice of using them to study physiological changes has opened up new lines of research, and reduced the need to work with higher animal models such as mice.

Professor Miguel-Aliaga crossed from one line of thought to the other when she found a group of neurons carrying nerve signals from the fruit fly's brain to its intestine.

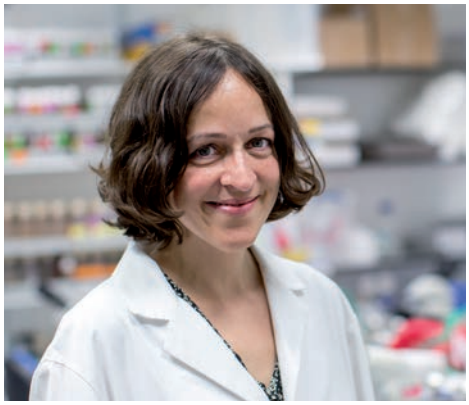
"I'm a developmental neurobiologist by training, so initially I was interested in how neurons acquire different identities when a nervous system is made," she explains. "But as I was doing that I stumbled upon this subset of neurons that innervate the gut, and I thought that was interesting. We know quite a lot about neurons that innervate muscles or bring in stimuli from the outside, but we didn't know very much about these neurons."

In order to find out more, researchers would need to single out these neurons, change the way they function and then follow the consequences in the intestine. In most animal models this represents a considerable hurdle, but in fruit flies it promised to be relatively straightforward.

First of all, fruit flies have a much simpler nervous system than higher animals. Then there are techniques that allow specific genes in the fly to be inactivated, or defined groups of neurons to be turned on or off. The functional consequences of these changes can then be tracked using physiological assays and biomarkers, or behavioural tests.

And just as humans share 60 per cent of their genes with the fruit fly, there are also similarities between human and fly intestines. Both, for example, contain stem cells that help replenish the lining of the gut, building it up if required or repairing damage. Discovered almost 20 years ago, this similarity has prompted a thriving line in research looking at subjects such as nutrition, stem cell biology and how the intestine deals with tumours. But not, until Professor Miguel-Aliaga's research, the nervous control of the gut.

"This work with *Drosophila* is a pretty powerful approach, because you can combine genetics with physiology and see the mechanisms underlying how tissues adapt, not just how they are made," says Professor Miguel-Aliaga.



In the eight years since first identifying this group of neurons leading to the gut, Professor Miguel-Aliaga has continued to explore what they can tell us about how the brain and the digestive system communicate. She now leads a laboratory specialising in gut signalling and metabolism, which since 2012 has been part of the MRC's Clinical Sciences Centre at Imperial.

Its work has produced some fascinating discoveries. Looking at the neurons themselves, the group has identified a sub-set that interacts with the system of tubules that distributes oxygen throughout the fly's body. "These neurons talk to this system and regulate the branching of the cells that deliver oxygen to the gut, and that seems to matter in adaptations to malnutrition," she says. "So this is a new mechanism that we have been able to find in flies and which might apply to humans and to their vascular systems."

"This work with Drosophila is a pretty powerful approach, because you can combine genetics with physiology and see the mechanisms underlying how tissues adapt."

Professor Miguel-Aliaga and her team have also looked at the characteristics of the gut and its lining, the epithelium. This has produced a surprising finding. “Males and females – whether flies, mice or humans – have different sex hormones, and that makes us different and makes organs in males and females function differently,” she explains. “What we found in the fly is that the intestine has an intrinsic sexual identity, so the cells of the epithelium know whether they are male or female.”

By turning genes on and off, it was possible to make gut epithelium cells masculine or feminine, and explore how this affected their behaviour. These changes could be made without altering the fly’s developmental history or its circulating hormones.

This opens up all sorts of interesting questions for further research. For instance, might this intrinsic sexual identity play a role in the different way males and females develop cancers? The stem cells of female fruit flies divide and multiply more readily than those in male flies, and when a fly’s genes are manipulated so that it develops tumours, females develop many more than males.

“This tells you that there are also sex differences in tumour susceptibilities,” says Professor Miguel-Aliaga, adding that this mirrors the incidence of human cancers. “People have traditionally ascribed this to sex hormones, but I think that, based on the fly data, it would be very interesting to go back to humans or to other model systems such as mice, and see whether there is some sort of intrinsic component to these differences in susceptibility.”

Another area of investigation that she would like to explore in more complex animals is the observation that the intestine increases in size when female flies are laying lots of eggs. “In flies we have seen that this remodelling of an adult organ is important for reproduction, so we want to see whether a similar process happens in mice, whether it happens through the same mechanisms and whether it matters for reproductive success.”

Rather than neurons, this change is down to a hormone. Released when the fly is laying eggs, the hormone appears to prepare the fly’s body for the additional energy demands of reproduction. This research has the potential to tell us more about how hormones prepare women’s bodies for pregnancy and recovery after giving birth.

Although studies involving fruit flies are covered by Imperial’s policy on animal research, they are not regulated under the Animals (Scientific Procedures) Act. Moving her research work from flies to mice is not something that Professor Miguel-Aliaga takes lightly.

“Working with fruit flies is not regulated in any way, whereas with mice that will be very different, and rightly so,” she says. “This is new to me, so I’m taking courses and I have to pass exams in order to work with mice.”

One advantage of carrying out so much research in flies is that subsequent studies in mice can be closely targeted, using far fewer animals. “We don’t have to start from scratch in mice,” Professor Miguel-Aliaga says. “We don’t have to carry out genetic screening, we can address very specific questions.”

> *“What we found in the fly is that the intestine has an intrinsic sexual identity, so the cells of the epithelium know whether they are male or female.”*

This is how the group intends to move forward. “Most people in the lab work only on *Drosophila*, and we find it a very useful discovery tool, where we can make progress relatively quickly. So that will continue to be the main focus,” she concludes. “I don’t think we will ever use the mouse as a first step, but we may want to go back and forth between the two systems. For example, if the mouse data points to something unexpected, we can explore its mechanism in flies, then go back again to the mouse model.”

LAY SCRUTINY

Putting animal welfare first

Non-scientists play a vital role in ensuring that animal research is conducted in an open, transparent and appropriate way. Chris Banks, Director of Library Services at Imperial, explains her voluntary involvement and the role of the Animal Welfare and Ethical Review Body (AWERB) committee at Imperial.

Chris Banks joined Imperial as Director of Library Services in September 2013 from a similar role at the University of Aberdeen. At that time, the College was already in the process of creating its Action Plan for world class animal research.

"When I came to Imperial, I met with Professor Maggie Dallman who chairs the central AWERB committee," Ms Banks explains. AWERB is a mandatory function for any organisation that carries out research involving animals. Every new application to conduct animal research, and every renewal, must be scrutinised by an AWERB.

"Each committee must include lay people – non-scientists – and I know that such people can be hard to find at an organisation like Imperial," Ms Banks says. "I sat on AWERB at Aberdeen and when I spoke to Maggie and offered to do the same here, she welcomed me enthusiastically."

"I have two degrees but they are both in music, so I consider myself to be very lay indeed!"

"Although I'm not technically required to, I do read all applications in full, and I am free to ask any questions I have."

"I see it as a privilege because when you receive medical treatments you don't know anything about what has gone into refining them. This involvement with AWERB gives me an insight into the process."

> *"As a lay person, I find it fascinating to learn about how science develops but ultimately, it's about balancing saving and improving lives with animal welfare."*

One insight, Ms Banks explains, is that researchers consistently look for any other way besides working with animals to do their work, if possible. "If they believe it is the only alternative, they use no more animals than are necessary but if there are other ways to do the science then those will be explored first."

She is also confident that researchers are putting a great deal of thought into the welfare of research animals. "These animals receive a very high level of care, and staff work to minimise suffering, create a natural environment and to get the numbers right."

For example, Ms Banks mentions a recent application where a medical researcher brought new insights from his experience of patient care to improve animal care.

In addition to providing independent scrutiny, lay committee members bring an additional skill. Each research application must be accompanied by a lay summary of the work. If the application is successful, this summary will appear on the Home Office website and must be comprehensible to anyone who is interested. "It's important to get the lay summary right," Ms Banks says.

Over the last year, Imperial has taken a new precaution of asking all staff whether they are working on projects where animal research is taking place outside the UK.

In 2015, Ms Banks attended an event organised jointly by the Laboratory Animal Science Association and the RSPCA. It was held to bring AWERB members from across the UK together. "It was an opportunity to share best practice. At Imperial we use a simple but helpful form to help us assess applications, including elements of the 3Rs and the quality of the lay summary. It's not required by the Home Office but it's useful and it's now being taken up elsewhere," she says.

AWERB committees also include animal technologists and vets. "I think there can be

tensions between senior researchers and more junior technologists, but because Central Biomedical Services staff comment on applications at AWERB, there's a good opportunity for concerns to be raised."

The committee also reviews work that has already been done and Ms Banks says this ensures a process of continuous improvement. "We gain experience and take the knowledge we've gained from each project on to the next."

Ms Banks's role on the group is voluntary but she says she is motivated by a personal experience. She says: "Some years ago, a member of my staff died of motor neurone disease. Then, as it happens, the next research proposal that I looked at was for a study of this disease. As a lay person, I find it fascinating to learn about how science develops but ultimately, it's about balancing saving and improving lives with animal welfare. My role, indeed the role of all of us, is about getting that balance right."

FOCUS

Zebrafish as windows to cell biology

This page: Dr Laurence Bugeon; above right, Dr Serge Mostowy, left, with a PhD student.

From respiratory disease to dysentery, researchers at Imperial are working with zebrafish to investigate how inflammatory immune responses affect the body, and how we could treat some of the world's most deadly diseases.

Young zebrafish are transparent, their skin and internal organs as clear as glass. This makes them remarkable subjects for research. With the aid of dyes and fluorescent tags, scientists use a microscope to see how their organs and even individual cells function, in an entirely non-invasive way.

Comparable observations of organs are very hard to achieve in mammals such as mice. "The procedures are very invasive, very complicated and don't get the same kind of data," says Dr Laurence Bugeon, a research fellow in Professor Maggie Dallman's laboratory in the Faculty of Natural Sciences, who uses zebrafish to study inflammation.

And at the cellular level, it is almost impossible to get the same results. "There are fantastic scientists on the planet using the mouse model, but they cannot see what we can see using the zebrafish model," says Dr Serge Mostowy, a research fellow in the Faculty of Medicine who uses the zebrafish to study how cells react to bacterial infection.

"What we can see is absolutely remarkable," he goes on, "not only at the whole animal level, but you can look at the single cell level, you can also look at the single bacterium level, and you can do this in a living organism, in real time."

Zebrafish also turn out to be a remarkably good model for conducting research into some aspects of human biology. For example, their innate immune system – the first line of defence against foreign bodies – is very close to that found in humans.

Their adaptive immunity, the defence system that recognises and targets foreign bodies in a trained and specific way, is different, and develops later. This means that researchers can use young zebrafish to examine the innate immune system in isolation.

Female zebrafish can lay hundreds of eggs at a time. Fertilised in the water, these quickly develop from embryos into larvae. They begin to feed independently after five days and reach adulthood after twenty eight days. A complete innate immune system is in place early in this process, so even quite young larvae can be used for research into its mechanisms. For studies involving specific organs, which take time to develop, older larvae or adults are required.

Dr Mostowy uses zebrafish larvae that are five days old or younger to study how cells respond to infection. "We've engineered transgenic fish in which proteins or cell types are labelled with fluorescent colours, and we can also infect these larvae with bacteria of different colours. Then we can watch the orchestration of host-pathogen interactions in real time using high resolution microscopes."

He is particularly interested in *Shigella flexneri*, a bacteria responsible for a form of dysentery in humans, which he showed can also infect zebrafish cells. *Shigella* kills over 1 million people per year, particularly in the developing world. It is also becoming increasingly resistant to conventional anti microbial drugs. "So we are looking for new and unique ways to control the bacterial infection."

One idea is to examine how the cytoskeleton, which is responsible for the internal organisation of cells, targets *Shigella* for destruction. This involves a family of proteins called septins, which assemble into cage-like structures and trap bacteria. "The septin cage recognises around 15 per cent of intracellular bacteria, so we are trying to find ways for it to recognise 100 per cent of the bacteria," Dr Mostowy says.

This research also tells us more about the basics of cell biology, since the proteins involved in restricting infection also play a role in key cellular processes such as cell division and the day-to-day management of the cell. "We can learn a lot about these proteins through the process of infection, and then apply that knowledge in uninfected cells."

When it comes to inflammation, the match between zebrafish and humans is also good. "We have found that the molecular pathways, and most of the mediators and molecules are the same," says Dr Bugeon.

"The septin cage recognises around 15 per cent of intracellular bacteria, so we are trying to find ways for it to recognise 100 per cent of the bacteria."

The similarity also extends to the way the fish's intestine deals with cholesterol. This allowed Dr Bugeon and her colleagues to watch as the fish's immune system responded to a high cholesterol diet, sending immune cells tagged with fluorescent markers to the gut.

They also filmed the muscle contractions, called peristalsis, that move food through the intestine. "This is a very complex movement, and you cannot image that in a mouse. But in the zebrafish, especially at a very early stage, we have beautiful videos of this peristalsis. And we found that it was affected after a high cholesterol diet," she says.

The next step is to understand the cause behind this effect, and to relate it to the disruption movement associated with gut inflammation in humans.

The Dallman Lab is also working on a zebrafish model for human respiratory disease. "The fish don't have lungs, but they have a respiratory system with a similar method of gas exchange to us, except they do it in water rather than air," Dr Bugeon says of the fish's gills.

The advantage of this model is that it is much easier to apply irritants and stimulants to a fish's gills, and observe the effects, than it would be with a mouse's lungs. Testing with cigarette smoke, bubbled through water, confirmed the idea. "The inflammation is similar, with the same molecules involved as in humans and mice."

It was also possible to see the same kind of structural change in the tissues after longer exposure, although this irreversible change in humans was reversible in fish. Understanding this process may indicate ways to regenerate and repair lung damage in humans.

The next step is to investigate how the zebrafish model might replicate infection with respiratory viruses.

The rules for carrying out research on zebrafish differ depending on how developed the fish are. In the first five days, before they feed independently, they are not covered by the Home Office regulations. After that, they are regulated like any other vertebrate animal, with the same emphasis on the 3Rs – the replacement, reduction and refinement of animal experiments.

Dr Mostowy mostly uses larvae that are five days old or younger in his procedures, and so is not formally regulated. "But in terms of organising our fish room, deciding which fish to breed and how to make transgenic fish we always consider the 3Rs," he says. "And in terms of statistics, we design experiments beforehand to determine how many embryos we need to address a question."

Welfare is also a consideration during procedures, even when the larvae are less than five days old. "For microscopy we don't want them to move, so we anaesthetise them. That means they also won't feel anything," he says.

"The larvae may only be two millimetres long, but they are regulated. That means we have to apply for every procedure that we do, and care for the fish in the best way we can."

Dr Bugeon works with older larvae and adult fish, since the organs that interest her have to be fully developed. "The larvae may only be two millimetres long, but they are regulated," she says. "That means we have to apply for every procedure that we do, and care for the fish in the best way we can."

She insists that using zebrafish should be seen as a refinement of animal procedures rather than replacement. "A fish is the same as a mouse. It can experience pain as well, and so we have to consider it in the same way. Just because fish are not furry and warm, it doesn't mean that we don't care."

ETHICS

Prioritising the 3Rs

The 3Rs (replacement, reduction and refinement) are enshrined in government licensing of animal research and are a major consideration in the mandatory ethical review process but, in line with its Action Plan, Imperial aims to go above and beyond what is required by law.

The 3Rs advisory group was set up in 2014 following a review of animal research governance at Imperial. Its aim is to develop and implement good 3Rs practice in all animal research at the College.

The group is chaired by Richard Reynolds, Professor of Cellular Neurobiology at Imperial. His research focuses on how multiple sclerosis develops and is Director of the UK Multiple Sclerosis Society Tissue Bank.

"The 3Rs committee is an advisory group with a remit to improve the 3Rs culture at the College and ensure it is taken up by everyone involved in this work," explains Professor Reynolds. He says the committee, which is made up of animal technologists and researchers at different stages of their careers, began by looking at how the 3Rs were already applied at Imperial. "This exercise showed that the application of the 3Rs is already good so we moved on to ask how we can improve on the baseline."

"We decided to begin with junior researchers. Project licence holders have got to be more aware of the 3Rs because their funding applications to charities and research councils require it. Personal licence holders are exposed less to the 3Rs and can therefore be less aware."

With this aim, Professor Reynolds and his team began a series of workshops aimed at junior researchers. He says: "Workshops can be thought-provoking and they lend themselves well to generating ideas. We wanted participants to come up with practical ways to improve the application of the 3Rs to their work."

Three workshops have taken place – the first with a group of Central Biomedical Services (CBS) staff, and the others with researchers working in surgery and cancer, and brain sciences. Four more have been planned covering infection and immunity, inflammation biology, endocrinology and diabetes, and bioengineering and material sciences.

"We split the workshops into smaller groups of people, give questions specific to their area and ask them to generate new ideas," Professor Reynolds says. "I have been very impressed with the number of ideas they come up with; things they had never thought of before."

"With our first group of CBS staff, they put their ideas on a spreadsheet which is now displayed in the rooms in our animal facilities."

Running the events, alongside Professor Reynolds and one of Imperial's vets, is Sarah Lane who is the Programme Manager for the 3Rs and Quality Assurance.

Ms Lane says this first workshop with animal technologists also provided an opportunity to talk about how communications between CBS staff and researchers could be improved in line with Imperial's Action Plan. "Staff who took part agreed that in some cases this was already very good but there were others where they needed to challenge the status quo to improve the 3Rs culture."

> *"Workshops can be thought-provoking and they lend themselves well to generating ideas. We wanted participants to come up with practical ways to improve the application of the 3Rs to their work."*

Several of the ideas generated could have a major impact on reducing the numbers of animals used. Ms Lane explains: "For example, tissue sharing is already done at Imperial's Hammersmith Campus but why not across all sites? It will create some logistical challenges but if we can match researchers who are offering tissue samples to those who need them for their work, we could reduce numbers overall."

Professor Reynolds believes that the workshops are having an effect on the 3Rs culture among researchers. "It's an important reminder for everyone who takes part. We have staff from all over the world working at Imperial – they come from different cultures and legislation in some parts of the world is less stringent. So for some there is a lot to learn."

Alongside these workshops, a programme of talks is planned. This will see researchers working in alternative species, such as flies and worms, presenting their approach to those working in higher animals such as mice or rats. Ms Lane says: "We hope that these sessions will stimulate ideas and show there are other possibilities to replace or refine animal experiments."

Professor Reynolds and the rest of the group are also responsible for running and short-listing the Provost's Awards for Excellence in Animal Research (see overleaf). He says: "The awards recognise and reward good practice by our staff and I am impressed by the number of applicants and the huge variation in the work they describe."

The ongoing role of the 3Rs committee is to look at new applications for licences to conduct animal research and renewals of existing licences.

"In conjunction with the Animal Welfare and Ethical Review Body (AWERB), I look at them all," says Professor Reynolds. "Researchers also have to say how they applied the 3Rs on previous licences so we have the opportunity to spot the need for improvement."

"Now the standard is very good. It has improved over last year thanks to the increased levels of awareness."

PROVOST'S AWARDS

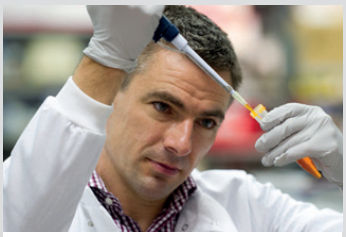
for Excellence in Animal Research

Since 2014, the Provost's Awards for Excellence in Animal Research have recognised best practice and acknowledged staff who have made advances in the 3Rs, shown openness or shown a long-term commitment to improving research practice. Winners receive £1,000 to cover costs of presenting their work to a wider audience.

Award winners for 2014

Application of the 3Rs, CBS staff: Miss Joanna Malton

Joanna Malton has been employed as a technician at Imperial for 15 years, working mainly with rats and mice, and more recently with guinea pigs. She undertook a study to understand why a particular strain of rats was consistently producing low weight offspring with a high mortality rate. Her work led to a change in how rats are housed, which in turn has led to healthier study models, which is better both for the animals themselves and for research.



Application of the 3Rs, researchers: Dr Michael Emerson

Dr Emerson has worked to refine animal models for studying thromboembolism and respiratory disease, reducing both severity and the number of mice used in a typical experiment. He was a co-author of the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines, the first set of guidelines for the reporting of animal studies. He also sits on the Ethics, Regulation and Public Involvement Committee of the Medical Research Council as the animal ethics expert, and has contributed to their new guidelines on the conduct of animal procedures.

Communication: Ms Amy Wathen

Amy Wathen has worked at Imperial for 14 years. Following an infiltration of animal facilities at the College by animal rights activists, she surveyed technicians, vets and managers on the impact of the experience, and gave a presentation called 'Surviving an infiltration' at the 2014 institute of Animal Technology Annual Congress.
Ms Wathen won a prize for best first-time presenter at the Congress, and she has subsequently been asked to speak to other groups, including the Home Office.

Lifetime achievement: Professor Andrew Rice

Professor Rice is a clinical academic who has held a personal licence for animal research for nearly 30 years and a project licence since 1995. He has spent much of his career improving animal models used in neuropathic pain research and enhancing their clinical relevance. He is a member of an NC3Rs working group looking at the impact of rodent age on study outcome. He has also advocated the use of the NC3R's ARRIVE reporting guidelines, and led international working groups on this topic in both Europe and North America.

Award winners for 2015

Application of the 3Rs, CBS staff: Ms Bruna Delfini

Since Bruna Delfini joined Imperial two years ago, she has become a mentor for Imperial's new Apprenticeship scheme, joined the College's 3Rs Environmental Enrichment committee, and improved communication between CBS and research staff. She has also applied her extensive experience in the care of zebrafish to practice at the College, through investigating methods for monitoring water quality and helping researchers to optimise the performance of fish housing systems.

She said: "Winning the prize was unexpected; in fact I didn't know I was even nominated by one of my colleagues. Thanks to this prize I feel appreciated and motivated in doing my job."

Application of the 3Rs, researchers: Dr Francesca Rauzi

Dr Rauzi's research, funded by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), develops improved models of cardiovascular and respiratory diseases. She has developed and refined a real-time monitoring technique of radio-labelled cells in animal models of thrombo-embolism and inflammation, which has led to a 75 per cent reduction in the number of mice used in particular experiments. Dr Rauzi located two research groups based in the US who she knew could be using it to reduce their use of mice, and persuaded those groups to collaborate with her.

Dr Rauzi has also been involved in public engagement activities in relation to her work, including taking part in a 3Rs talk at a "Pint of Science" event.

Communications: Ms Natasha Martineau

Natasha Martineau is Head of Research Communications at Imperial. Over the last two years, she has ensured that Imperial has met and surpassed its commitment to the Concordat on openness in animal research, through initiatives including the College's first interactive events where the public could discuss animal research with technicians, vets and scientists, and editing the Animal Research Annual Report.

Ms Martineau said: "It's been tremendously rewarding for me to work alongside the people who care for and work with animals at Imperial, as well as those whose support we need to carry out this work, such as security staff and College senior leadership. It is their willingness and commitment to openness that has made this work possible."

Lifetime achievement: Ms Angela Kerton (joint winner)

As Named Veterinary Surgeon at Imperial, Angela Kerton has spent 15 years providing ethical and welfare advice on project applications. She currently leads a team of veterinary surgeons to share best practice and promote the 3Rs. Initiatives she has promoted include: a switch from injectable to gaseous anaesthetic agents; the promotion of the use of oral analgesics for rodents; the creation of dedicated animal score sheets and post-operative care check lists; and improved training in the recognition of signs of pain and distress.

Ms Kerton said: "As Named Veterinary Surgeon, the College's support has inspired me to help others within our large and varied laboratory animal science community."

Lifetime achievement: Professor Uta Griesenbach (joint winner)

Professor Griesenbach's research at Imperial over the last 18 years has contributed to developing gene therapy treatments for respiratory diseases. This work has led to the recent completion of a trial of gene therapy in cystic fibrosis patients. The success of this research is underpinned by animal studies and Professor Griesenbach has worked to reduce the number of animals required and developed models to replace animals. For example she has used lung cells and tissue in the lab as well as intact human lungs that have been rejected for transplant.

She said: "It is a great honour to receive this award, which underlines our conscientious use of animal models."

FOCUS

Imaging: The future of animal research?

Technological advancements in biological imaging in animal research are improving animal welfare and the accuracy of clinical data. Imperial's Professor Eric Aboagye explains how improvements to imaging are changing the future of both animal research and medical procedures.

The world is getting wise to the usefulness of imaging in pre-clinical research, according to Professor Aboagye. "It's best to use these technologies, both from an animal welfare perspective but also in terms of the high-quality research we can do to understand and treat disease."

Aboagye is Professor of Cancer Pharmacology and Molecular Imaging at Imperial, and a champion of the College's new Biological Imaging Centre. This opened in 2015, bringing together facilities previously housed in the Medical Research Council's (MRC)Cyclotron Building at Imperial's Hammersmith Campus.

The move was prompted by the decision to demolish the MRC Cyclotron Building, making the facilities homeless. "It's an important resource, and a lot of us were very keen that we didn't lose time in setting up the new centre," says Professor Aboagye.

On the one hand, techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) get researchers closer to the things they need to study, rather than using proxies. "So if you want to study cardiac motion then you can study cardiac motion in a living animal, rather than something that is less relevant to you," Professor Aboagye says.

And on the other, they can reduce the number of animals used in experiments and refine procedures to make them less distressing. "The critical thing is that we can generate more data from the same animal, or use smaller numbers of animals to get the same amount of data, without compromising welfare."

Studies involving infectious diseases provide a good example. In the past, a large group of rats or mice would be followed as they developed an illness, with samples of the population sacrificed and examined at set intervals to see how far the infection had progressed. This would continue until the infection had run its course.

Now the progress of the infection can be followed visually, over a series of days or weeks, in the same small set of animals. "You can visualise the disease pathology, you can look at the impact of drug treatment on that pathology, and that really makes a lot of difference," says Professor Aboagye. Following developments in the same animals also means you are comparing like with like, which helps control for natural variations in the way individuals respond to infection.

Imaging can also improve welfare for the smaller number of animals involved in experiments. For example, it may be possible to end experiments sooner, which can be more humane. "You can see the disease evolving and decide at day two, for example, that it has evolved sufficiently that you don't need to wait the four days before the animal becomes ill."

Researchers may also be able to avoid invasive procedures such as taking biopsies. "You already have a high-resolution image of the pathology. So it is a less invasive method and you can see pretty much the entire animal."

Some of the techniques offered by the Biological Imaging Centre, such as biophotonic imaging, are specifically designed for animal studies. Others, such the MRI and PET, employ instruments that are essentially miniature versions of those used for medical imaging of people. The main difference is that the animals need to be anaesthetised for most imaging work. This keeps them still during the process and lessens their distress.

Animals coming to the Centre first go into holding rooms where they can acclimatise before receiving the anaesthetic. "We need to be quick, to look after the animals and weigh them properly, to know how much anaesthetic to give them," Professor Aboagye explains. "And we need to be able to monitor the animal during anaesthesia, to ensure they have the right respiration and cardiovascular activity."

After imaging, the animals go to recovery stations where they can regain consciousness in a warm and quiet environment. They are then moved back to the holding rooms where they are monitored to ensure they have fully recovered, and are eating and drinking normally.

Depending on the procedure involved, they are then returned to their usual living quarters, or kept for another round of imaging in the following days.

Knowing how anaesthesia affects the animals is an important part of this process, both for their welfare and for the research results. "Different anaesthetics can potentially cause depression of respiration, can affect the cardiovascular system, and the regulation of temperature, especially in small animals such as rodents." At present, the Centre only works with rats and mice.

Professor Aboagye's own research with the Centre includes studies that will improve medical imaging in cancer patients. For example, current methods of screening for gastroenteropancreatic neuroendocrine tumours (cancers in hormone-producing nerve cells along the gut or in the pancreas) are typically slow and produce poor results.

"In most hospitals, patients come in, they get an injection, they go away and come back in two or three days for the scan, which is fuzzy at best. So we have been trying to develop a probe that allows us to give patients a scan within an hour or so of coming in, and produces high-quality images."

First, in vitro tests narrowed down the range of possible probes for the cancer, for instance eliminating those likely to be broken down too easily in the body. Then the two best candidates were tested in detail on mice with human tumours, to see what image quality they produced.

The probe with the greatest sensitivity, and which produced the best images of primary tumours, also turned out to be taken up strongly in the liver. This was a problem, since metastatic tumours in these conditions tend to turn up in the liver, and so would not be seen. The other probe had slightly less sensitivity, yet was still very high, but it also gave a very low background signal in the liver.

"Tumour signal to normal organ background is a difficult concept to model in vitro," Professor Aboagye explains, "so doing the animal experiments helped us to focus on one candidate, which at this stage is doing very well in clinical studies."

For the future, Professor Aboagye thinks that enhanced techniques will improve the contribution imaging can make to animal welfare. For instance, Imperial's Centre is the first in the country to use a cryogenic coil with its MRI, a device that improves signal strength 2.5 times over background noise.

"That doesn't sound a lot, but in MRI terms that's huge," he says. "It allows us either to get higher resolution data in the same scanning time, or to back off in terms of time, as much as five fold." Reducing the time that animals spend in the scanner reduces the time they spend anaesthetised and the risks of dehydration, for example.

Meanwhile ultrasound may offer possibilities for imaging without anaesthetic, and perhaps setting up imaging stations in buildings where animals are usually housed, avoiding the need to move them.

A further initiative would involve doing more to make images accessible to the wider scientific community, perhaps through a secure online archive. This would allow researchers to see the original three-dimensional images, over the whole period of a scan, rather than the two-dimensional snapshots often used to illustrate scientific papers.

Having more detailed information could allow researchers to eliminate unnecessary repeat experiments or reduce the number of animals they need to use in their own work.

"Tumour signal to normal organ background is a difficult concept to model in vitro, so doing the animal experiments helped us to focus on one candidate."

COMMUNICATING

about animal research

Since 2014, staff across the College have worked together to develop and grow Imperial's communications on animal research and build on the commitments that were made as part of the Concordat on Openness in Animal Research.

As well as a range of public and outreach events, Imperial staff took opportunities to share their knowledge and insights with peers across universities, charities, research funders, learned societies and commercial companies at seminars and group sessions. There was also recognition of Imperial's work to ensure open communication around research with animals, as College staff received several awards for initiatives including the website, film and Imperial's first annual report on animal research.

Outreach and public engagement

In early 2015, the launch of the first report on animal research was marked by a public event that gave visitors the chance to meet vets and technicians who care for animals at the College, and to hear from scientists and doctors about how and why animals are used in research. Part of Imperial's Fringe series, the event featured a range of exhibits including material on how stem cells are being used to provide alternatives to animal research in the study of heart conditions, and how and why mice, rats, fish and other species are still used in research to improve human and animal health. An interactive exhibition run by the Central Biomedical Services (CBS) team at the Imperial Festival in both 2015 and 2016 gave alumni and members of the public the chance to explore how animals are cared for and housed. During the summer of 2015, one of the College's animal facilities opened its doors to a school visit for the first time, as a group of 16- and 17-year-olds were taken on a tour by technicians. The students saw how mice and rabbits are housed and looked after, before taking part in a practical lesson, co-ordinated by the College's Outreach team, working with Daphnia – tiny freshwater animals – to measure the effect of caffeine or alcohol on heart rate.

Sharing expertise

In tandem with work to engage the public in communications around animal research, staff from the College went out to speak to the wider research community and share lessons learned from Imperial's work in this area. In May 2015, five Imperial staff attended a meeting for all signatories of the Concordat, to share their own experiences. The meeting brought together animal technicians, employees from the Home Office, RSPCA, scientists and animal retailers to discuss the broad question: 'How can we support research organisations to be more open about their use of animals in science?' Discussions focused on the practical steps that organisations had taken, where there were barriers to openness and how these could be overcome in practice. In June 2015, Terry Branch, Imperial's Head of Security, travelled to Cardiff University to present at a seminar on security issues linked to working with animals to attendees from Cardiff and seven other universities. In September 2015, Head of Research Communications, Natasha Martineau and Director of CBS, Mandy Thorpe spoke at the Biotechnology and Biological Sciences Research Council's Pirbright Institute, where they outlined the journey Imperial has taken to improve its communications on animal research; and in November 2015, Imperial's News Editor, Kerry Noble, spoke at the Institute of Cancer Research about Imperial's internal and external communications.

Recognition

As work to increase the effectiveness of Imperial's communications became manifest, the College was awarded a number of prizes in recognition of these efforts, including a Heist award for best communications or PR campaign for initiatives including internal communications, public events, the new website, film and annual report. The work was described by judges as "a brave campaign, the results of which should be beneficial for both medical research and animal welfare". The College also received an Understanding Animal Research commendation for the website. Kerry Noble said: "It's great to receive recognition for our work on openness in animal research. The quality of the website is a testament to all the Imperial staff who work with animals and their willingness to tell their stories, and appear in photos and video."

THE CONCORDAT

on Openness on Animal Research

By signing the Concordat on Openness on Animal Research, Imperial has made the following commitments:

Commitment 1:

We will be clear about when, how and why we use animals in research

Commitment 2:

We will enhance our communications with the media and the public about our research using animals

Commitment 3:

We will be proactive in providing opportunities for the public to find out about research using animals

Commitment 4:

We will report on progress annually and share our experiences

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This publication is produced for Imperial's public audiences, and our funders, collaborators, staff, students and alumni. It is part of our commitment to report annually on progress with implementing our Action Plan for world-class animal research, and forms part of activities to communicate more widely about our animal research.

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www.imperial.ac.uk/animal-research