



# THE CHANGING FACE OF PRIMATE RESEARCH

*A hard-won political victory for primate research is at risk of unravelling in pockets of Europe.*

BY ALISON ABBOTT

**T**he worst moment in neuroscientist Andreas Kreiter's 16-year struggle to defend his research came when his wife arrived home after the birth of their second child. Waiting for her was an envelope containing a death threat against their three-year-old.

Kreiter, who uses macaques in his studies of the brain at the University of Bremen in Germany, is a veteran of the fierce and periodically violent tactics of animal-rights activists. When protests peaked in the late 1990s, he lived under police protection — but he still continued his research. "I had thought very carefully before deciding to work with primates," he says. "And I believe it is necessary if we are to understand the human brain."

Later Kreiter found himself facing an unfamiliar foe: local authorities looking to restrict primate research in their city. In 2008, Bremen officials declined to renew Kreiter's licence to

work with macaques. The fate of his research has been in legal limbo ever since.

Kreiter's courtroom conflicts put him in good company. Across Europe, a particularly volatile patchwork of emerging local regulations threatens to distort the spirit of a recent European Union (EU) directive that explicitly allows research on non-human primates. Although some researchers say they have never felt so secure, others are facing new obstacles as activists change tack, from bullying researchers to putting pressure on regional policy-makers.

The problems continue even as the EU is pushing for the translation of basic research into therapies — a transition that often requires the testing of experimental therapies in primates. And opportunities for translational research are growing thanks to recent technological breakthroughs. However, restrictions on primate experiments could hinder their development.

ILLUSTRATION BY GARY NEILL

Some European researchers are shifting their strategies, too, by talking more openly about their work with primates. But other scientists have simply stopped using monkeys altogether — or side-stepped the European quagmire by setting up controversial collaborations in other countries, particularly in Asia.

“Primate researchers should always expect to be under pressure, because we are handling a valuable and sensitive resource,” says Roger Lemon of University College London, UK, who hopes his work on how the brain controls fine hand movements might lead to therapies for recovering function after a stroke. “But it’s a sad irony that key developments may be transferring to countries that don’t have the high level of animal welfare we have here.”

### STABILIZING STEP

The pressures on primate researchers have taken many forms. In the United States, for example, commercial airlines have effectively ceased all primate shipments by air within the country, making it difficult for researchers to transport animals. Many airlines in Europe have taken similar steps, but Air France continues to provide service.

Not long ago, the EU seemed to take a step towards stabilizing the environment for primate research. In September 2010, after more than a decade of anguished public debate, the EU adopted a directive governing the use of animals for research purposes. With its careful balance of animal-welfare and research needs, the directive seemed destined to ease tensions. Among other things, it established minimum welfare requirements for all animals, laid out definitions of pain intensity, and banned most research on great apes. It also included a hard-won clause — added at the last minute after intense lobbying by the biomedical community — explicitly permitting basic research on non-human primates, provided the work could not be carried out in any other species.

EU member states were required to anchor the directive into national legislation by 1 January 2013. And they were forbidden to ‘gold-plate’ the regulation by making national law stricter than EU law.

But animal-rights activists have continued their fight. They have honed their activities for greater media attention and have delayed implementation of the directive in several countries. Animal-rights organizations now focus on policy-makers rather than scientists, says Robert Molenaar, campaign manager for the Coalition Against Animal Experiments (ADC), which operates in the Netherlands and Belgium. The ADC is concentrating first on monkey research in universities, he says, because it is an easy way to get press coverage and influence political opinion.

The ADC is also forging international links and works closely with a sister organization in the United Kingdom, the Anti Vivisection Coalition (AVC), headed by Luke Steele.

Steele spent nine months in prison after being convicted in 2012 of harassing staff at Harlan Laboratories, a contract research company in Blackthorn, UK. The jail time was interesting, he says: he used it to reflect on strategies. “Researchers themselves tend to be traditionalists who are not open to alternatives,” he says. “I realised we need to go for policy-makers.”

The AVC and the ADC were the main driv-

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ers of the Stop Vivisection Initiative, a petition calling for the EU animal-research directive to be abrogated and animal research to be banned altogether. The petition, launched in November 2012, collected more than a million signatures across the EU within a year. The signatures are now being verified; if they pass, the initiative will be granted hearings at the European Commission and the European Parliament.

“This will reopen the debate — something we’d all rather do without, given the enormous effort that the commission, scientists and animal-welfare groups invested in achieving the compromise,” says Stefan Treue, director of the German Primate Center in Göttingen and an adviser to the European Commission on the 2010 directive.

Treue doubts that the Stop Vivisection campaign will change European legislation — political demand for new therapies is too strong, he says. But, like many of his colleagues, he says that researchers working with monkeys should abandon their conventional tactic of keeping quiet, which cedes ground to the activists. Two months after the directive was approved, Treue helped to launch the Basel Declaration (see *Nature* 468, 742; 2010), which commits its signatories — so far more than 2,500 — to be open about their animal research and to engage in public dialogue.

The declaration prompted a sea change, and many initiatives are emerging in its wake. For example, the Swiss Primate Competence Center for Research was launched last year in Fribourg to provide a training centre for scientists and technicians wanting to work with primates, and an educational one-stop shop for the public.

Individual scientists are also speaking up on their websites. Neuroscientist Pieter Roelfsema at the Netherlands Institute for Neuroscience in Amsterdam, who works with monkeys, says that so far activists have not targeted research in his lab. But he fears this may soon change.

Last spring, minority parties in the Dutch parliament — including the Dutch Party for the Animals — posed formal questions about whether research using monkeys is necessary, if it could be replaced by alternative methods, and if the number of government-funded research institutes using monkeys could be reduced.

With these developments in mind, Roelfsema is planning a public-information webpage about the value of primate research, modelled on that of Nikos Logothetis, a director at the Max Planck Institute for Biological Cybernetics in Tübingen, Germany. Logothetis’s site, which has thousands of visitors a week, emerged from a public-relations debacle. In 2009, he invited a team of investigative journalists from a national television company into his lab, imagining that the reporters would be impressed by his monkeys’ luxurious accommodation, and surprised by how relaxed and content the animals seemed. Instead, the journalists portrayed a slightly mad scientist among suffering animals. The experience “spectacularly demonstrated the need for a reaction of scientific organizations to the escalating absurdity of the anti-vivisectionists”, Logothetis says.

However, Tübingen — unlike Kreiter’s Bremen — is a city where researchers enjoy a supportive political environment. Even the city’s mayor, a member of the Green Party, which is not known for supporting animal experiments, has openly criticized flyers distributed by activists as untruthful, and described the harsh treatment of Logothetis as “unacceptable”.

“This shows the power of local politics to influence how easy or difficult it can be to carry out research using monkeys in different European regions,” says Treue, whose research centre also benefits from local political support in Göttingen. For scientists such as Treue, the EU directive has brought a feeling of stability.

### THE ITALIAN JOB

That feeling is largely absent in Italy. In 2012, activists attacked a beagle-breeding facility near Brescia. It was later closed down. In 2013, they sabotaged experiments at the University of Milan. And last month, activists posted flyers that included photographs, addresses and phone numbers of some of the university’s researchers in their home neighbourhoods.

By 2012, some populist politicians had adopted the animal-rights cause and used it to influence the Italian implementation of the EU directive. The proposed law went beyond the directive, calling for a ban on xenotransplantation and the use of animals in addiction research.

Italian scientists woke up late to the threat, and by the time researchers had organized a petition defending animal research — signed by 13,000 people in just a few weeks — the course of the distinctly gold-plated law was already set. It passed through parliament in December.

Researchers who use monkeys are also worried about ambiguities in how the Italian law





Animal-rights campaigners have switched from targeting scientists to putting pressure on policy-makers.

interprets the EU directive's clause allowing research on non-human primates. "It's not clear at all whether basic research is allowed or not," says neurophysiologist Roberto Caminiti at the University of Rome La Sapienza, who chairs the Committee on Animals in Research for the Federation of European Neuroscience Societies.

The law also requires all research proposals involving non-human primates, cats or dogs to be authorized by the High Health Council (Consiglio Superiore di Sanità), the broad mandate of which includes drug licensing and approval of clinical protocols. This additional level of control, on top of the approval required from local ethical committees, would slow and destabilize the process, says Caminiti.

The legislation is expected to become law in March. As soon as it does, Caminiti and his colleagues plan to file an appeal to the EU Court of Justice. "Gold-plating is not allowed," he says, "so we are confident of winning." In the meantime, Caminiti predicts that Italian labs working with primates will all be able to argue that their work has health benefits for humans.

In Belgium, the government is hurrying through a similar gold-plating decree that would also ban the use of primates in addiction studies, and require a national committee to approve projects involving non-human primates, even after approval by local ethics committees. The Belgian health minister would have the final say on whether a particular project could go ahead, raising concerns that final decisions would be based on politics, rather than on science or ethics.

Political decisions are already affecting

research in Switzerland, a non-EU country that is not bound by the 2010 animal-rights directive. In 2000, Switzerland's constitution was changed to protect the dignity of animals — a move that led courts to limit the use of monkeys to translational research.

Researchers in Fribourg have been able to continue their studies of spinal-cord repair in primates, but local authorities in Zurich have not renewed licences for basic research using primates since 2004. Kevan Martin, a director at the city's Institute of Neuroinformatics, had to stop mapping the functional microcircuitry of the macaque brain in 2006, when his licence expired. Martin was shocked to learn that local authorities had declined to renew his licence because the work was unlikely to reap practical benefits for society in the near term. He was even more shocked when his appeal to Switzerland's supreme court was turned down. "Is any applied research possible without basic research?" he muses.

#### WORKING ABROAD

In this climate, some Swiss scientists are relying on their collaborations in other countries to carry out primate experiments. Botond Roska of the Friedrich Miescher Institute for Biomedical Research in Basel and his colleagues have used mice to develop an experimental treatment for a common type of blindness called retinitis pigmentosa. The method is now poised for human trials, to be run by the small Paris-based biomedical company GenSight Biologics, which Roska co-founded. "But you can't go directly from mice to humans because you can't be sure if the neural circuits are the

same," says Roska. "Mice are simply not a good model of how people see."

Rather than face uncertainty in Switzerland, Roska and his collaborators — GenSight and the Vision Institute in Paris — are conducting primate studies in France, where animal activists have less political support. Roska hopes the first human patient could be treated within the year.

Like Roska, Per-Olof Berggren at the Karolinska Institute in Stockholm has reached a translational turning point in his research. He has developed an experimental therapy for diabetes in mice, and now needs to test it in primates before moving to humans. He thinks he could have got a licence for this in Sweden, but knew that he could not have afforded it. Regulations in the country, where animal-rights and animal-welfare groups are very powerful, require particularly large, sophisticated — and consequently expensive — primate facilities. So Berggren decided to do the work in Singapore, where he says facilities are first-class and ethical standards are as high as in Europe. "They have a long tradition of working with monkeys there, and it doesn't cost so very much."

Berggren is far from alone: many European researchers are taking their primate research to Asia, sparking a controversy that is dividing the scientific community. Some worry that standards of ethical oversight and animal welfare could be lower in certain Asian countries. And Martin points out that the trend exacerbates the loss of skills already apparent as the number of groups working on primates in Europe falls. (The number of primates used in the EU for scientific purposes shrank by more than 25% between 2008 and 2011, according to the European Commission.) "The loss is going to be much harder to reverse," he says. "Finding anaesthetists and surgeons has already become more difficult."

One European scientist, recently returned from two weeks at a leading institute in China, says that he found many Europeans setting up collaborations there — but they, like him, did not want to say so openly, for fear of damaging the reputations of their home institutions.

The scientist insists that ethical concerns are out of place, and that standards at the institutes match those of Germany and the United States. "It is not a question of low standards but of forward-looking research," he says. "And it is nice to enjoy the energy and optimism, and not always hear the word 'no'."

Back in Bremen, Kreiter still hopes to hear a 'yes' in court. With the support — moral and financial — of his university, he has spent more than five years fighting local authorities in a string of courtroom battles. He is now awaiting yet another verdict from a high court in Leipzig. "It may be the last," he says. "But you never know how things will develop." ■ **SEE EDITORIAL P.5**

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