

BPRC's Research Achievements

The contribution of research with monkeys
to progress in medical science



Inhoud

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Human life expectancy has increased tremendously over the last fifty years. People now live longer, and often in better health. One key factor in this positive development has been the availability of medicines and vaccines.

A healthy human body is a complex balance between various organs. If something goes wrong, we become ill. Sometimes the cause is clear, such as when the body is invaded by a virus or parasite. We do not know exactly what causes some diseases; some examples are auto-immune conditions such as multiple sclerosis or arthritis. But because nobody wants to be sick, we must continue to develop improved medicines and treatments.

Medicines and treatments require research. Much of this kind of research is performed in laboratories, but eventually the theoretical concepts must be put into practice. Does the medicine work? And is it safe? Unfortunately, answering these questions still requires animal testing. Simple aspirin tablets, complex bone-marrow transplants, and even the National Vaccination Programme (something we all take for granted) are all the products of research conducted on animals.

What is important to realise is that groundbreaking treatments are never the result of a single animal test – every test performed worldwide is but a tiny part of a large system capable of producing new treatments for patients.

Monkeys

Approximately 0.05% of all animal tests in the Netherlands are performed on monkeys. Although this is a small percentage, without it medical science would not be where it is today.

Research on monkeys is ethically complex because of the sympathy we feel for them. Monkeys and humans are very similar, both inside and out. This is why research on monkeys is sometimes necessary, particularly when researching the immune and central nervous systems.

About BPRC

The Biomedical Primate Research Centre (BPRC) is a specialist scientific research institute. BPRC conducts research on three species of monkey: rhesus macaques, long-tailed macaques and common marmosets. We have years of experience in researching diseases that constitute a serious threat to public health. These include infectious diseases such as malaria, HIV/AIDS, hepatitis and tuberculosis; conditions of later life such as Parkinson's and Alzheimer's disease; and autoimmune disorders such as multiple sclerosis. BPRC has also been closely involved in a study designed to improve organ transplantation methods.



Top: rhesus macaque, left: long-tailed macaque, right: common marmoset.

Research

BPRC's research focuses primarily on:

- the emergence and improved understanding of diseases, allowing us to establish and improve the effectiveness and/or safety of medicines, vaccines and treatment methods; and
- the efficacy and safety of new medicines, vaccines and treatments.

The 3Rs:

Our research is governed by the principle of the 3Rs: Refine, Reduce and Replace.

Refine

All monkeys at BPRC live in social groups housed in spacious accommodations. They are born into these groups and raised by their parents, which reduces their stress levels. We observe their behaviour to learn how they respond to each other and to us, and our training programmes are designed around these observations. This approach prevents stress during studies, and the animals offer their cooperation willingly. Our veterinarians are constantly searching for even better animal treatments, analgesics and anaesthetics.



Reduce

We share our research results with scientists across the globe, which helps prevent the same experiment from being repeated unnecessarily. We strive to obtain the best possible results from the fewest possible animals, and in a manner that is as animal-friendly as possible.

Replace

Our ultimate hope is to eliminate animal testing from research entirely, which is why BPRC always investigates alternative research methods. See under 'The 3Rs and animal welfare' for more details on these efforts.

More information

We regularly post news items on our website, which cover a range of topics relevant to our field of work. More detailed scientific reporting can be found in our list of publications.

www.bprc.nl/en



Chronic illnesses

Patients with conditions such as multiple sclerosis or arthritis only visit the doctor if they experience symptoms. By that time, however, the condition has already been progressing for some time. Investigating the early stages of disease requires animal testing, as the animal models developed can also be used to test the efficacy and safety of drugs. The research conducted by institutes such as BPRC gives specialists an early opportunity to identify potentially serious side effects of new drugs used to treat chronic illnesses, such as multiple sclerosis and arthritis. See below for an overview of concrete research activities and results.

Parkinson's disease

Patients with Parkinson's disease have a shortage of a certain neurotransmitter in the brain called 'dopamine'. This shortage affects muscular control, causing patients to tremble and move more slowly. Current medications are not adequate, and cause a lot of side effects. In the Netherlands, around 50,000 people suffer from Parkinson's disease.

- The model for Parkinson's disease in marmosets has allowed us to identify connections between different areas of the brain. These connections can be used to circumvent the affected brain cells, allowing the cause to be compensated for and the symptoms of Parkinson's disease to be prevented. Data on these neural connections is aiding the development of new methods for treating Parkinson's disease.
- We have developed a new treatment model against chronic Parkinson's in marmosets, which suppresses the symptoms of the disease via neuro-feedback.

Alzheimer's disease

Alzheimer's disease is a condition of later life that affects the memory. It is a form of dementia, and is caused by the deterioration of nerve cells in the brain. Scientists assume that this is due to the accumulation of what are called 'beta-amyloid proteins' in the brain. Alzheimer's disease is the most common form of dementia, and affects 165,000 people in the Netherlands.

- We have set up a model in marmosets designed to improve our understanding of the disease. Just like humans, these monkeys also develop these protein 'plaques' later in their lives, allowing us to incorporate the natural course of the disease into the animal model. The model can also be used to develop and test new candidate drugs for efficacy and safety.

Post-traumatic stress disorder (PTSD)

Our day-to-day lives are full of stressful experiences, which can include threats, disasters, or even domestic violence, abuse or traffic accidents. We retain a clear memory of stressful experiences, so that we can avoid similar situations in the future. In some cases, however, they overwhelm the memory and disrupt ordinary life. This is called post-traumatic stress disorder (PTSD), and is a chronic anxiety condition. PTSD affects the memory and concentration, sleeping patterns, and has long-term effects on stress-regulation hormones.

- We have developed a new model in marmosets in order to study emotional memory, which allows us to identify which substances and areas in the brain are involved in memory storage. The model enables the investigation of processes within the brain, and the development of new treatments and drugs for combating PTSD.

Multiple sclerosis

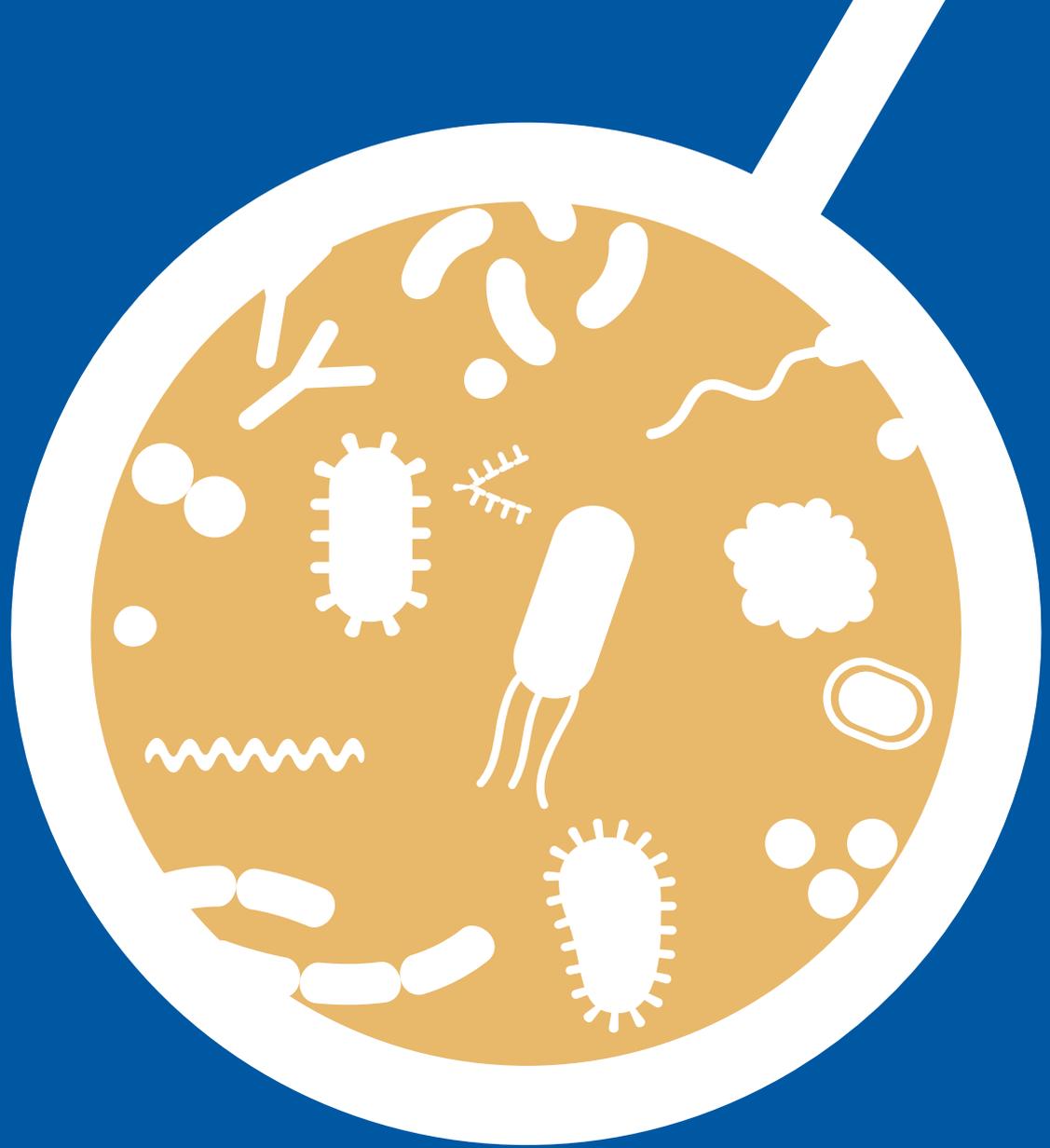
Multiple sclerosis (MS) is a condition that damages the protective layer of insulation surrounding the nerves in the brain, the spinal cord and the optic nerves, causing problems with locomotion, sensitivity and vision (among other functions). The progression of the disease varies from patient to patient, and is difficult to predict. In the Netherlands, around 17,000 people have MS.

- There are still many unanswered questions surrounding the progression and treatment of the disease. Research by BPRC conducted on rhesus macaques has provided new information on the potential mechanisms at play in the course of MS, contributing to the development and evaluation of new treatment methods.
- In marmosets we have developed a highly refined model of MS, which has supplied a possible explanation for the correlation between infection with the Epstein-Barr virus and the onset of MS, which until now was not well-understood.
- The MS model in marmosets helps us to understand the onset and the mechanism involved in the progression of the disease, offering prospects for new treatment methods.
- We have already tested a number of potential pre-clinical therapeutic antibodies for safety and efficacy in the BPRC MS models.

Rheumatoid arthritis

Rheumatoid arthritis is a form of joint inflammation. It is an auto-immune disease: the body's immune system turns on itself. It is a chronic illness that can progress in a variety of ways. In the Netherlands, around 250,000 people suffer from rheumatoid arthritis.

- Research on monkeys has delivered a wealth of scientific data on the onset of joint inflammation. For example, it is now clear which key factors contribute to a high susceptibility to joint inflammation.
- We have demonstrated that antibodies targeting collagen (the cartilage protein) in the joints of human patients with rheumatoid arthritis correlates strongly to the arthritis models in monkeys.
- Using the model of arthritis developed in rhesus macaques, we have been able to test various promising new treatments. Further development has now shifted to the clinic, and so this model has now been put in reserve.
- We also developed a model for chronic arthritis in marmosets.



Infectious diseases

The research spectrum of infectious diseases is constantly in flux. What is unknown today may become a threat tomorrow. The contribution that primates make to research into infectious diseases cannot be underestimated. Medicines to combat HIV, hepatitis and malaria are all based on primate research. We have also made significant strides in the battle against tuberculosis. However, emerging infectious diseases require the development of new medicines.

Malaria

Malaria is caused by a parasite that enters the body via mosquito bites. Around half a million people die annually of malaria, most of whom are young children.

- The malaria parasite has a complicated life cycle, and malaria in monkeys has provided new insights that have proved useful in the development of drugs and vaccines.
- Universities are currently testing the first Dutch vaccine against Malaria tropica in humans, following successful primate tests by BPRC.
- BPRC has contributed to the development of new malaria treatments which are currently being tested by clinic researchers.
- BPRC participated in research that revealed a new approach to developing anti-malarial drugs.
- Research in monkeys demonstrated that one particular candidate vaccine would produce too many side effects in humans, and so research on the drug was terminated.
- Some malaria parasites can remain hidden inside our bodies. These are called 'dormant' parasites. Thanks to the genetically-modified malaria parasites developed by BPRC in monkeys, we now have a better understanding of exactly what dormant parasites look like. We carefully documented the genetic code of these parasites and made the results freely available to science, allowing other researchers to work on new drugs.
- BPRC has provided genetic material from a strain of monkey malaria that is increasingly infecting humans. This material can be used by researchers for clinical diagnostic tests.
- BPRC has developed a new method for demonstrating whenever a specific part of a bonobo's immune system is compromised, most likely due to infection by a malaria parasite.

Viruses

The flu (influenza), AIDS (HIV) and hepatitis (hepatitis A, B and C) are all caused by viruses. Viruses transmitted by mosquitoes also constitute an ever-growing threat, through channels such as international trade and tourism, but also aspects such as climate change.

Hepatitis

Two kinds of liver infections can be caused by hepatitis: the brief, acute kind (caused by hepatitis A and E viruses) and the long-term, dormant kind (caused by hepatitis B, C, D and E viruses). Patients with the latter type only start showing symptoms during a late stage of the disease, due to the enormous reserve capacity of the human liver. Many people do not even realise they are infected, which allows the virus to do untold damage and ultimately cause cirrhosis and/or cancer of the liver.

- Hepatitis B is a serious liver condition. The current vaccine used in the National Vaccination Programme was tested on monkeys at BPRC, and now protects millions worldwide against this infectious disease.
- For a long time, we at BPRC also hoped to be able to develop a hepatitis C vaccine. Unfortunately, the hepatitis C virus is 'smarter'. We worked on the virus from 1982 until 2016. Sadly no vaccine was produced, however the data we collected did aid the development of antiviral drugs that are now part of the standard health insurance package.
- Researchers at BPRC detected and described a specific form of the hepatitis virus (hepatitis delta) which, along with the hepatitis B virus, can cause liver cancer.

HIV and AIDS

HIV, the virus that causes AIDS, is a major problem. Around 35 million patients worldwide are infected with HIV, and around 1 million die each year. Because research on monkeys lies at the very foundation of everything we know about HIV and AIDS, it is difficult to highlight only a few aspects here. Thanks to primate research, we now know how clever the virus is, and how it can be suppressed using antiviral drugs. Unfortunately not everybody has access to these drugs, and development of a vaccine has proven more difficult than first thought.

- Thanks to research at BPRC, we know that there is a correlation between the number of HIV viruses in the blood and the likelihood of actually developing AIDS. Doctors all over the world use this information to predict how the disease will progress, and to fine-tune personalised antiviral treatments accordingly.
- Chimpanzees can contract HIV, but unlike humans, they do not develop AIDS. We now know why, and this has given us new information about the course of this serious infectious disease.
- Before the protective effects of new vaccines can be tested in humans, they must first be tested in animals. In the case of HIV, monkeys were the only suitable candidates.
- Human DNA affects how vaccines work, and primate research has shown that HIV is no exception.
- One promising peptide vaccine offered partial protection against HIV and AIDS in infected rhesus macaques. We are now working to further develop this concept.
- HIV patients must currently take antiviral drugs for the rest of their lives to suppress the virus. One other potential strategy is called ‘therapeutic vaccination’, which involves training the immune system to keep the virus under control in the long term. We tested this idea in our rhesus macaques, and it is now being applied worldwide.

Influenza

Influenza affects millions each year, with potentially serious consequences in children and the elderly. Around 650 thousand people die of influenza annually. Current vaccination and vaccine production methods are inadequate.

- The influenza virus infection models that we have established in monkeys have provided greater insight and enable us to research anti-viral medicines and vaccines.
- Comparing different primate species has allowed us to develop the most suitable influenza infection model.

Viruses transmitted by mosquitoes

Mosquitoes are not only irritating, they are also well-known vectors of disease. In addition to malaria parasites, mosquitoes can also transmit viruses. Dengue fever, West Nile virus, yellow fever and the Zika virus are but a few examples. Each year an estimated 150 thousand people die prematurely from complications caused by mosquito-spread viruses.

- BPRC has developed West Nile virus infection models in monkeys that can be used to study antiviral drugs and vaccines. Using these models, BPRC successfully tested a new vaccine that protects against infection.
- BPRC has set up two new models for key viral infections – dengue fever and Zika – which are being used to research antiviral drugs and vaccines.
- We have refined the model for dengue fever, and use it to test antiviral drugs.
- We have also developed a model for Rift Valley fever in marmosets, and have used it to test a vaccine.

Viral diagnostics

BPRC provides virological screening for monkeys worldwide, and discovers new primate viruses in animals from zoos and rehabilitation centres.

Tuberculosis

Tuberculosis (TB) is an extremely contagious lung condition caused by bacteria. It is estimated that tuberculosis causes one death every twenty seconds. The World Health Organisation (WHO) considers tuberculosis to be one of the greatest medical threats, due in part to the multiple drug resistance of the bacterium, as well as large number of infected individuals who are unaware (a quarter of the global population).

- BPRC helped lay the groundwork for the standardised application of macaques in a) pre-clinical research on the efficacy of new vaccines, and b) new vaccination strategies against TB.
- BPRC has determined that the efficacy of the only available TB vaccine – BCG – varies from one macaque population to another, and is comparable to what we see in humans.
- Research by BPRC confirms the predictive value of the TB model in macaques – aspects of tuberculosis observed in humans have also been observed in experimental tuberculosis infections in macaques.
- TB vaccination research by BPRC contributes to the prioritisation, selection and development of new candidate vaccines for clinical research.
- BPRC works continually to refine TB research, to reduce the discomfort that animals experience due to experimental infection. As research continues, we gain more information about the mechanisms of the illness and immune protection. One example is the use of scanning technology (PET-CT) that enables us to track the course of the disease.
- TB researchers at BPRC have demonstrated the ability to protect rhesus macaques against both infection and the disease using an alternative BCG vaccination route, that runs via the airways instead of the skin. These results encourage further research into the development of new TB vaccination strategies in humans.
- Our research on existing and improved preventive TB vaccination in macaques has produced new information on the immune processes that seem to play a part in protecting against tuberculosis.

Other bacterial infections

- BPRC has developed a new model in rhesus macaques for studying infections with the multiresistant bacterium *Staphylococcus aureus* (MRSA), as well as for investigating new treatments.



The 3Rs and animal welfare

BPRC believes in the importance of the 3Rs (Reduce, Refine, Replace). We do our utmost to keep laboratory animal numbers to a minimum, and to make the lives of the monkeys as comfortable as possible. You can be assured that our research is conducted with all possible care, and in accordance with the legal frameworks set out by the Dutch Experiments on Animals Act and European directives.

We also actively promote the use of alternatives to animal testing, and see the development of such alternatives as part of our mission. This is where new technologies and improved selection methods play an important part, as shown by the results on the next pages.

Reduce

- BPRC has developed new systems for cultivating strains of malaria that affect monkeys, creating the first-ever opportunities to research and develop treatments against the 'dormant' stages of the malaria parasite. These systems have drastically reduced the number of monkeys required for such studies.
- We have genetic background information on all monkeys at BPRC, which enables better selection for the various types of research. We are also developing new methods that rapidly and efficiently target specific aspects of the immune system. This ultimately reduces the number of animals required, makes us better able to select animals for the right studies and to apply the results to human populations.
- The Dutch Society for the Protection of Animals nominated BPRC's research on new malaria treatments for the Leaders in the Lab award (Lef in het Lab).
- Our laboratory researchers have developed cell-cultivation methods in order to study diseases of the central nervous system, such as multiple sclerosis (MS). These methods allow us to research the diseases without the direct need for an animal model. The knowledge gained is also used to refine animal testing methods, and has effectively reduced the number of animals required for research.

Refine

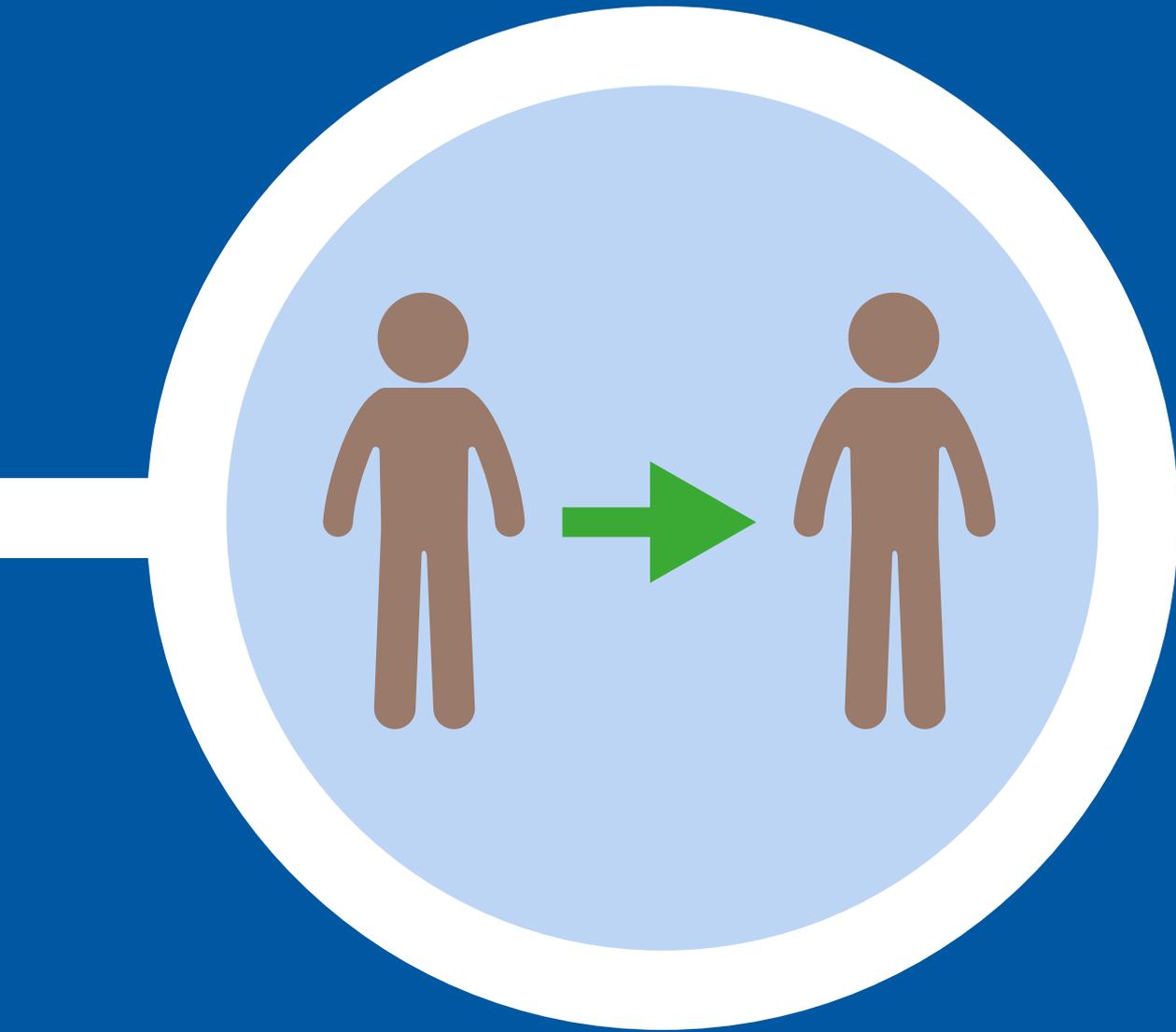
- BPRC has established a laboratory method for the testing and development of adjuvants (substances added to vaccines to increase their efficacy). This research was nominated for the 'Public Award for Alternatives to Animal Testing'. The resulting adjuvant is more animal-friendly due to its lack of side effects.
- Comparing various analgesic and anaesthetic treatments has enabled us to develop the methods best suited for use in marmosets.
- Marmosets cannot raise three young simultaneously. BPRC has therefore drawn up new breeding guidelines based on its own research, which serve to prevent the birth of triplets as much as possible.

- BPRC has developed methods for observing the course of multiple sclerosis (in marmosets) and arthritis (in rhesus macaques) that are significantly more animal-friendly.
- In tuberculosis research, BPRC identified the correlation between blood values and the likelihood of an individual surviving the illness. This information enables us to terminate some studies sooner, and makes the process less stressful for the monkeys.
- New methods have been developed for breeding and housing monkeys in research institutions. These methods reproduce the animals' natural habitats as closely as possible, significantly improving their welfare levels.
- The accommodation for rhesus monkeys at BPRC was awarded the Animal Testing Alternatives award (Alternatieven voor dierproeven).
- BPRC has staff who actively use Positive Reinforcement Training to reduce or eliminate stress in our monkeys. This form of refinement has a positive influence on both animal welfare and the experimental studies themselves.
- We have established (and continue to develop) an extensive enrichment programme for our animals that includes both food and non-food aspects.
- BPRC plays an important part in educating animal carers and other specialists in the field of animal training and enrichment, and runs national and international conferences on the improvement of monkey welfare in primate centres and research institutes.
- BPRC has written an enrichment manual. It used to be available on request in printed form, but is now also available online for free.
- We use contraceptives to regulate the number of animals born, while taking care to minimise disruptions to the animals' complex social structure.
- BPRC develops non-invasive and less invasive methods for the detection of specific markers, such as a new test that measures the long-term effects of stress using hair. These results show that animals experience far less stress, resulting from the combination of modern accommodations and a well-considered approach.

- BPRC has developed a method of DNA analysis for studying monkeys in the wild, which eliminates the need for animal interventions and improves animal conservation efforts in the wild.
- BPRC runs routine laboratory tests in order to detect abnormalities quickly and effectively, and to respond quickly if necessary.

Replace

- In addition to animal models, BPRC also uses cell cultivation techniques to test new additives in vaccines.
- A 'bioassay' is a testing method that makes use of cells that divide indefinitely. These cell lines have been infused with molecules and luminous proteins of various types, which eliminate the need for animal testing while still providing detailed information on the efficacy and safety of vaccines.
- Tissue and blood products obtained from monkeys are stored in well-documented biobanks. Many international researchers make use of these facilities, which serve to promote the 3Rs concept.
- Our research using cell-cultivation techniques is unravelling the tissue-specific properties of brain cells.
- At regular times, BPRC organises symposiums and scientific meetings on various topics, including alternatives to primate testing and the refinement of research methods.



Transplants; common good in the clinic

Primates have made a significant contribution to research on organ and tissue transplants, and the prevention of rejection responses. BPRC has been involved in this research since its very beginnings, and stood at the cradle of bone-marrow transplants. The knowledge obtained in part through research on primates has fuelled significant improvements in transplantation, which is now a reliable clinical procedure. This type of research now takes place almost entirely without using primates.

Organ transplants

- Specific genetic characteristics in humans play a very important role in the survival of transplanted organs. Selecting the most suitable donor for a patient in practice is now much easier thanks to the studies conducted in primates.
- In monkeys, we observed that preceding a transplant with a blood transfusion has a positive effect on the survival chances of the transplanted organ. Specialists now apply this knowledge in practice.
- The first drugs used to prevent organ rejection in humans (immunosuppressants) were first tested extensively on other primates. Any new anti-rejection treatment methods (such as different drug combinations) now undergo the same procedure.
- In humans, working according to a certain transplantation method increases the likelihood that the new organ will be accepted. The results from primate research have allowed us to determine which methods are safe and effective in practice.
- Studies on skin and kidney transplants in primates have resulted in new treatment methods that reduce rejection responses.

Bone marrow transplants

- Drugs are an important factor in ensuring the success of transplants. Several drugs that stimulate the production of blood cells following a bone marrow transplant were first tested in monkeys.
- Acute rejection responses can occur following a bone marrow transplant. One factor that can influence the severity of this response is the bacteria in the intestine (microflora). Modifying the body's microflora can help to limit rejection responses. Various hospitals now successfully apply this method, following extensive research in monkeys.

