Biomedical Primate Research Centre
Annual Scientific Report 2017

Welcome
Join our journey through health research and alternatives

Biomedical Primate Research Centre

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Monkey Research

- Explained -

Welcome to the 2017 annual report from Biomedical Primate Research Centre (BPRC). Biomedical research in monkeys is still a necessity. This was concluded by the European Commission after extensive background research and in this report we proudly present our contribution to science and development of alternatives.

In this report our scientists inform you about their work with monkeys and their most important scientific findings. As you will see our work covers many different aspects, that we collaborate with (inter)national partners and that our research is often funded by (inter) national agencies. Together, this highlights that our science and standards of animal wefare are internationally recognized as high standard and scientifically relevant.

On January 1st 2017 BPRC housed 1596 animals, that is 1174 rhesus macaques (Macaca mulatta), 256 cynomolgus monkeys (long-tailed macaques; Macaca fascicularis), and 166 common marmosets (Callithrix jacchus). On December 31st BPRC housed 1536 monkeys, 1082 rhesus macaques, 260 long-tailed macaques and 194 common marmosets.

In 2017 BPRC worked with 315 animals, 232 rhesus macaques, 42 long-tailed macaques and 41 common marmosets. Like any Dutch research institute that works with animals BPRC has reported these numbers to the NVWA. More information on the necessity of animal research is provided by SID. Read more.

The goal of BPRC is to understand life-threatening diseases, and to develop and test therapies to treat or prevent these diseases. In addition, BPRC is an expertise centre for development of the 3Rs, Replacement, Reduction and Refinement.

BPRC focuses on diseases for which certain aspects cannot be studied in humans, and other alternatives than biomedical research in monkeys, are not yet available. Most (infectious) diseases start without clinical symptoms. When a patient finally seeks medical help, the actual disease-process is already ongoing and caused damage to cells and/or organs. Early disease processes can only be studied when the disease or infection is experimentally induced and controlled. We use this knowledge to develop better vaccines or medicines.

Monkey Research

- Explained -

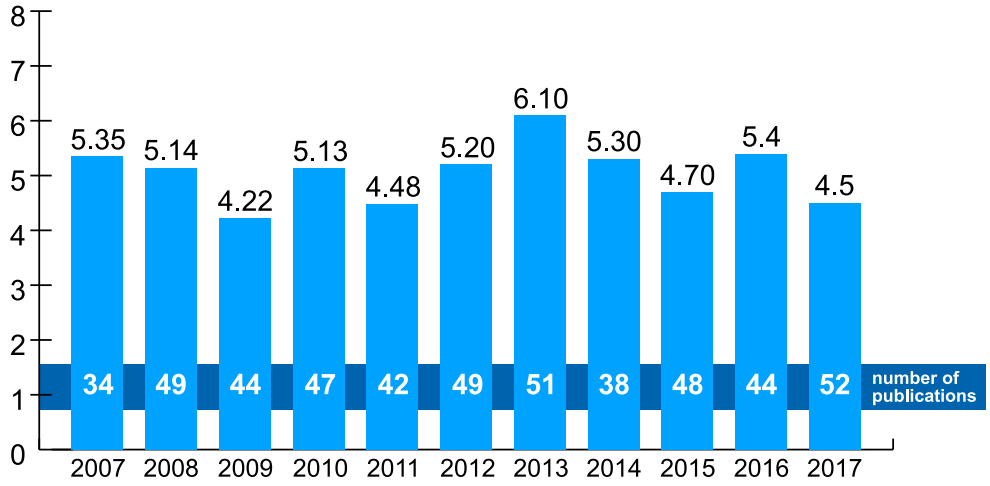
Infectious diseases like aids, influenza, malaria and tuberculosis (TB), killed 2.8 million people in the year 2017. This means every 8 seconds a person died of one of these potentially preventable diseases. In addition to infectious diseases, chronic degenerative diseases, like multiple sclerosis (MS) and Parkinson's disease (PD), are increasing due to ageing societies. To limit the number of people that suffer from these infections and diseases new vaccines and new drugs are needed. The development of vaccines and drugs is a long and winding road. It requires detailed information on the disease processes, and potential vaccine or drug candidates need to be tested for efficacy. Most testing is done in test tubes. However, we need to confirm safety1 and efficacy in an appropriate animal model that is comparable to the infection or disease in humans. This stage is called the preclinical phase.

1 Please note that safety in this context refers to safety in the mode of action. This is not the same as determining the batch-to-batch variation in vaccines or drugs that are already approved for human or veterinary use. Animal-free alternative methods for batch-to-batch quality control for approved vaccines or drugs are awaiting approval from regulatory agencies. BPRC does not perform batch-to-batch quality control experiments.

To increase the transparency in the use of laboratory animals in The Netherlands, the Dutch Government installed the Centrale Commissie Dierproeven (CCD). The CCD is the legal body in The Netherlands that is authorized to provide licenses. The use of animals in experiments is strictly regulated in Europe, Directive 2010/63/EU. In The Netherlands this is described in the Wet op de dierproeven. The law is in line with the principles of the 3Rs. In our institute, we actively work on the 3Rs at all levels, departments and research units. BPRC is accredited by AAALAC International. This accreditation guarantees good institutional policies, animal husbandry and welfare, veterinary care and physical BPRC plant.
Read more

Message from the board

The first important event in early 2017, was the successful PhD defense of one of our veterinarians at the University of Utrecht. Later in the year, another PhD defense of a staff-member took place at the University of Groningen. Our scientific output continues steadily and BPRC researchers published several important papers in high ranking journals. One of the highlights was the description of a new orangutan species in Borneo. This study was done in collaboration with members form our Department of Virology. Overall, the BPRC staff published in 2017 52 scientific papers with an average impact factor of 4,5.



Last year the BPRC was several times in the news. Our open-door policy is generally appreciated as is manifested by the BBC documentary “the monkey lab”. Moreover, more than 700 people visited our facilities and premises.

We made progress with regard to animal welfare issues. In 2017 we e.g. focused on further training of the animals to minimize stress during experiments, started with renewal of the marmoset breeding facility to further optimize housing, and refined our methods for anesthesia of marmosets.

We will strive to improve even further the quality of our work and its results, and will maintain the vision to play a guiding role in the field of Replacement, Reduction, and Refinement, as well as animal welfare.

Message from the board

The Supervisory Board and the director congratulate the scientific and supporting staff with the obtained results and recommend reading this annual report. Of course to scientists, but certainly also to the public, policy makers and politicians.

Prof. dr. R.E. Bontrop
Director of BPRC

Mr. J. Vrolijk
Chairman of the Supervisory Board

Our Financial Results

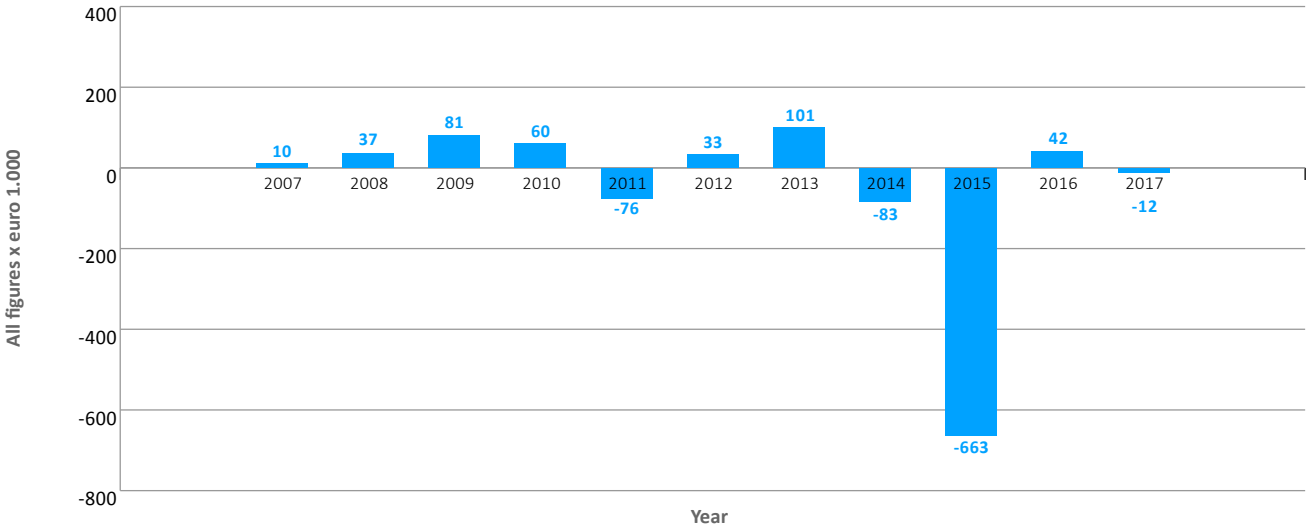
In 2017 BPRC closed the financial year with a small negative financial result of 12K EUR. This is a significant achievement, as previous years were characterized by a gradual decline in income.

Due to the base grand from OCW, BPRC is able to maintain the academic staffing up to standard and to keep the support and facility components of the organization at a desired level to facilitate:

Research necessary to combat life-threatening and debilitating diseases in humans, which could be a threat to general public health.
Animal welfare and the development of animal free research methods.

The BPRC financial annual report has been audited and approved by a financial accountant.

Result development BPRC 2007-2017



Our Financial Results

PROFIT AND LOSS ACCOUNT

	2017 (K€)	2016 (K€)
Turnover projects (external)	4.458	4.609
Turnover projects (subsidy)	7.079	5.825
Total turnover projects	11.537	10.434
Other excluding interest	1.102	1.246
	1.102	1.246
Total turnover	12.639	11.680
External direct project costs	912	538
Staff costs	7.782	7.321
Depreciation	396	421
Other operating charges	3.570	3.393
Total operating costs	12.660	11.673
Profit/loss on ordinary activities	21-	7
Interest	9	35
Profit for the financial year	12-	42
Tax	-	-
Profit for the financial year after tax	12-	42

EFFECTIVE PERSONNEL

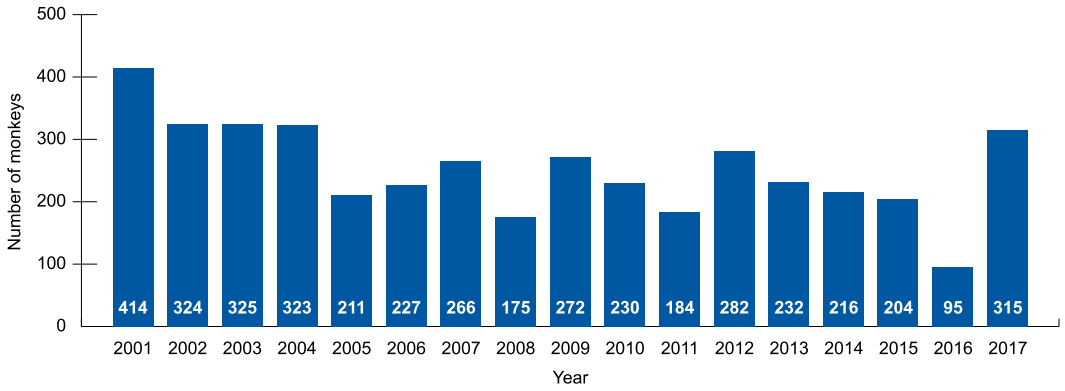
	2017		2016	
Service Departments	14,9	14%	15,9	16%
Animal Science Department	46,8	44%	42,1	42%
Research	44,8	42%	41,6	42%
Total	106,5	100%	99,6	100%

BALANCE SHEET 31 DECEMBER

	2017 (K€)		2016 (K€)	
ASSETS				
FIXED ASSETS				
Buildings and structures	32.847		34.741	
Tangible fixed assets	1.668		1.682	
		34.515		36.423
CURRENT ASSETS				
STOCKS		47		62
DEBTORS DUE WITHIN ONE YEAR				
Work in progress	227		999	
Receivables from contracts	521		220	
Receivables tax	828		19	
Other receivables	182		127	
		1.758		1.365
Cash at bank and in hand		18.309		17.952
Total assets		54.629		55.802

	2017 (K€)		2016 (K€)	
LIABILITIES				
EQUITY				
Equity	1.715		1.673	
Revaluation reserve buildings	9.994		7.750	
Result current year	12-		42	
		11.697		9.465
PROVISIONS				
Primates	-		-	
Deferred tax liabilities	-		-	
(Flexibel) retirement	-		-	
Repairs buidings	2.847		5.875	
		2.847		5.875
LONG TERM DEBTS				
Bank	23.330		24.264	
Received in advance on assets	9.120		9.784	
		32.450		34.048
SHORT TERM DEBTS				
Received in advance on projects	2.508		1.332	
Received in advance on assets	361		406	
Received in advance subsidy	173		173	
Accounts Payable (TAX)	606		587	
(Flexibel) retirement	-		-	
Accounts Payable	1.470		1.397	
Commitment Bank	933		889	
Other liabilities	1.584		1.630	
		7.635		6.414
Total liabilities		54.629		55.802

Facts & figures



The number of monkeys we worked with over the years and the scientific achievements in 2017.

A total of

52 scientific publications

in international journals. Complete list

A

Tuberculosis vaccine

works better after inhalation.

New

animal-free methods

to study diseases in the brain.

New

HIV vaccine

ready for testing in people.

New drug-targets for

difficult-to-treat-malaria

parasites.

Potential treatment for

Parkinson's disease

patiens.

New insights in what a

perfect flu vaccine

should do.

We are ready for

mosquito-borne virus

health issues.

999 new drugs tested by

animal-free methods

to treat malaria.

Facts & figures

But there is more:

To obtain

more knowledge from less animals

we recruited more academic staff.

We welcomed

750 guests in 31 groups

on informative guided tours at BPRC.

We placed

25 updates on our website

in the newsfeed.

We delivered

2 PhDs

who graduated after successful dissertation of their PhD thesis.

We performed

50,000 viral diagnostic tests

for zoos, sanctuaries and other clients.

We supervised

13 bachelor or master students

during their internship.

BPRC's Research Areas

Modeling potentially life-threatening human diseases in non-human primates requires extended knowledge and dedication in animal care taking, colony management and translational research. Scientists from BPRC are world-wide acknowledged for their expertise in the translation of human diseases caused by viruses and parasites to non-human primates, as well as autoimmune diseases and genetics.

Research Areas
Alternatives

When a disease cannot be studied in humans, scientists can induce experimental diseases in animals. The more closely the animal species is related, the better the disease processes resemble that of humans. Although this approach has led to many important discoveries and new therapies, this approach also may have an impact on the welfare of animals. We are fully aware of our responsibility to society and animals and we are only allowed to use animals when there are no other -alternative- methods available. Alternative methods are categorized along the principle of the 3Rs of **R**eplacement, **R**eduction and **R**efinement, all of which have a place within BPRC. When alternative methods are available, Dutch law obliges researchers to use the alternatives and forbids the use of animals. However, not many of such methods are available yet. Rather than waiting, BPRC is actively testing and developing alternative methods. The 3Rs are implemented in the research of every department, as well as in the separate Unit Alternatives.

3Rs throughout BPRC

Replacement

In 2009 BPRC-researchers developed an new in vitro assay to test drugs for anti-malaria activity. This assay replaces the use of monkeys. Last year we tested 33 new potential anti-malaria drugs with this assay. Before 2009, 33 monkeys would have been necessary to test these 33 compounds. So far, BPRC tested 999 drugs with the animal-free assay.

Reduction

Genetics; genes play an important role in infections and diseases. We have implemented new techniques to determine the genetic background of animals in the breeding and experimental colonies. This enables us to select (or deselect) appropriate animals to answer particular research questions. For example; we know that certain genes play a role in the development of AIDS after HIV infection. We now know that these genes are also present in monkeys. Selection of animals for an HIV experiment is therefore based on these genes. Proper selection reduces the variation in an experiment and therefore smaller group sizes are required to obtain statistical significant differences.

Research Areas
Alternatives

We work hard to reduce the number of animals we work with. Optimizing and standardizing in vitro laboratory tests plays an important role in this. Also in 2017 we have implemented new techniques. By using these new conditions, we aim at less variation in laboratory test that will lead to smaller group sizes in our animal experiments.

Refinement

Improving animal welfare is a continuous process in our institute and BPRC staff take part in (inter)national training programs to remain their high standards. In 2017 this resulted in:

- All animals were socially housed
- 25 animal caretakers used positive reinforcement training (PRT). They train their animals twice per week. With this training method we were able to perform certain biotechnical techniques without sedating the animal
  - In 2017 all marmosets were trained to voluntarily jump on a scale to obtain body weight without sedation.
  - All experimentally housed animals were trained to drink from a syringe, thus voluntarily take oral medication.
- Caretakers spent 15% of their time on (cage)-enrichment. For instance assembling food-puzzels, providing animals with toys or redecorate enclosures.
- Further improvements were implemented in diet variation, to maximize natural feeding routines.
- New methods were implemented to monitor stress levels;
  - Hair samples were obtained to measure cortisol levels
  - Pictures were taken to measure Alopecia
  - Round the clock camera recordings to get insight in behavior of less-compatible pair-housed animals, in the absence of a caretaker
- In 2017 an improved version of the 'Welzijnsevaluaties' was implemented
- New features were introduced in our monkey database for the registration of animals.

All animals in experiments are observed at least twice a day. During this observation different parameters are 'scored'. Under control conditions an animal shows a broad variety of natural behaviors. In some models for (infectious) diseases the animal's behavior

Research Areas
Alternatives

changes. This is however a subjective parameter and changes are difficult to observe. We currently investigate the options for objective measurements of physical activity with telemetry that registers X-Y-Z coordinates of individual animals. With these devices it is also possible to measure body temperature, heartrate, blood pressure. This will lead to further refinement of our animal models.

In 2016 the Bill and Melinda Gates Foundation announced that the tuberculosis-research performed at BPRC is of such high standard that we will serve as one of the three central facilities for the testing of TB vaccines, world-wide. As part of this initiative the Bill and Melinda Gates Foundation initiated and funded a new line of tuberculosis-research at BPRC. For this purpose, a PET/CT scan was installed in 2017. Implementation of this novel and non-invasive technique allows screening of tuberculosis-disease progression over time. This will not only lead to new scientific insights and better understanding of tuberculosis-disease progression, it may also lead to standardizing protocols and methods that are used world-wide to evaluate vaccine candidates, and therefore minimize the number of non-human primates used for TB research.

3Rs Alternatives Unit BPRC

Developing *in vitro* methods for the central nervous system

People are getting older. In an aging population people suffer from age-related diseases. Many of these diseases, like Alzheimer's disease, Parkinson's disease and multiple sclerosis affect the central nervous system. BPRC works with animal models for each of these diseases. *In vitro* methods to complement, refine, reduce and finally replace the use of animals are therefore highly relevant. Over the years we successfully developed methods to study individual brain cells in test tubes. In 2017 we have employed a new PhD student to push this development forward and to develop better and animal-free methods to study diseases of the central nervous system.

Research Areas
Alternatives

VAC2VAC: a European initiative

Vaccines are the greatest success story of biomedical science. Vaccines have changed human life expectancy dramatically. Experimental research on animals is not only used during the development phase of vaccines, but also during the production and quality control phase. Vaccines are typically produced in batches. Every batch undergoes the same strict series of animal tests before it is released. We participate in a European initiative, VAC2VAC, that tries to change this. The idea is that every new batch of a vaccine should not be treated as an entirely new entity, but rather as one of a series. This implies that every new batch only needs to be similar to the previous batch, and should not be tested in animals. To prove similarity between batches, animal-free methods are used. By adding our panel of in-house engineered cell lines to the consortium we characterized several different vaccines and batches in 2017. Our results demonstrate that different batches are indeed highly similar according to our tests. Together with the tests that are developed in other European labs, this initiative should lead to abandoning animal testing in vaccine batch release.

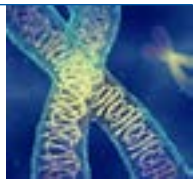
Read more:

Alternatives for animal studies: BPRC participates in European project

Research Areas
Ethology

Monkeys are social animals. Understanding the behavior of monkeys helps us to recognize deviation in behavior. This is not only important for scientific behaviour research but also to manage our breeding and experimental colony. We work together with a group of behavioral scientists from the University of Utrecht to improve our knowledge.

Post-mating processes and generating MHC-heterozygous individuals



Every individual has two sets of chromosomes, one from the father and one from the mother. These chromosomes carry our genes. Some genes play an important role in our immunological defense system. Having two different genes (heterozygosity) means that your immune system can fight more invading pathogens than when you have two copies of the same gene (homozygosity). It is believed that there are biological mechanisms that influence the choice of mating-partner, so that your offspring ends up being heterozygous. But what if parents have partially the same genes? For instance when the mother has genes A and B and the father A and C. Are there post-mating processes, like differential gamete selection and fetal/infant survival, that prevents their offspring from receiving two copies of the same A gene? To answer this question, we tested a group of rhesus macaques by looking at their mating behavior and analyzing their genes. In the offspring of parents with shared genes we found similar numbers of homozygotes and heterozygotes. Therefore, post-mating processes are not involved in generating MHC-heterozygous individuals.

Read more:

No postcopulatory selection against MHC-homozygous offspring: Evidence from a pedigreed captive rhesus macaque colony

Research Areas
Ethology

Social tolerance is associated with the evolution of sophisticated cognitive skills

Different monkey species differ in social tolerance. Some are socially tolerant while others are more violent towards each other. At BPRC we have two different macaque species. One species is known as tolerant and social the other as less tolerant. In The University of Portsmouth and in a sanctuary in Italy they have other macaque species. We investigated how the level of social tolerance related to their behavior in social and non-social tasks. Our behavioral scientists worked with the monkeys and came to the conclusion that all four macaque groups performed similar in the non-social tasks. But during the social tasks, the tolerant species performed better and were better in controlling their impulses compared to the less tolerant species. These outcomes support the idea that social tolerance is associated with the evolution of sophisticated cognitive skill that are relevant for cooperative social living.

Read more:

Comparing physical and social cognitive skills in macaque species with different degrees of social tolerance

Research Areas

General Primate Biology & Welfare

We work hard to maintain our healthy, stable and self-sustainable breeding colonies. The monkeys live in social groups that recognize their natural behavior and social structure.

Over the years BPRC staff-members have become experts in genetically and socially match making. This needs for a joint effort between BPRCs veterinarian staff, behavioral scientists, laboratory staff and experts in genetics. The stability of the breeding groups is normally reflected by the number of animals born. In 2017 124 rhesus macaques, 33 long-tailed macaques and 46 common marmosets were registered. This highlights the success of BPRC staff to compose a socially stable environment for monkeys.
To keep our animals in good physical condition we monitor the animals for their general health. We have a team of animal care takers, veterinarians, para-veterinarians and laboratory staff . In 2017 the expertise of this team was underlined by the fact that one of the veterinarians was chosen as the president of the association of European Primate Veterinarians. Read more

Moreover, we serve as a helpdesk for zoos, breeding facilities, sanctuaries like Stichting Aap and (inter)national research institutes when it comes to general health care of non-human primates. Our Primate Viral Diagnostics unit performed over 50,000 diagnostic tests for external professionals.

Research Areas

General Primate Biology & Welfare

Highlights in 2017:

One of our staff members successfully defended a PhD thesis entitled 'Veterinary care and welfare management in common marmosets' University of Utrecht.
Read more

Scientific publication in collaboration with veterinarians Stichting Aap; Thrombotic thrombocytopenic purpura related to ADAMTS13 deficiency, and successful treatment in a chimpanzee (Pan troglodytes verus).
Read more

Together with a Wildlife Research Centre in Saudi Arabia we found evidence for coronavirus infection in baboons.
Read more

A world-wide network from orangutan conservation biologists discovered a new orangutan species.
Read more

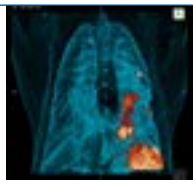
Research Areas

Tuberculosis

Tuberculosis (TB) is a bacterial infection that mainly affects the lung. Many people believe that TB is an old disease that was eliminated in the middle of the 20th century. Nothing could be further from the truth. TB is currently the deadliest infectious disease in the world. TB killed 1.7 million people in 2016 and over 10 million people fell ill from TB. 25% of the world population is latently infected with TB.

It is also believed that TB is a disease that can be treated with the current antibiotics. Unfortunately multiple-drug resistant TB-bacteria are increasing and more and more TB infected people cannot be treated. Vaccination is the only means to break the cycle of TB transmission and infection. At this moment BCG is the only vaccine that is approved for use in people but it is not very effective. BPRC is one of the three central facilities in the world for testing new TB vaccines.

PET/CT imaging technique



For the evaluation of new vaccine candidates, we need animal models that represent all the disease manifestations of tuberculosis in humans. BPRC has developed TB models in rhesus monkeys and cynomolgus monkeys to learn more about how the disease develops. We have learned that TB in the rhesus monkey develops as a progressive active form of the disease while infection of cynomolgus monkeys with TB can develop as a latent disease. We use both models to evaluate new treatments of TB. The TB group is continuously implementing new techniques for a more detailed analysis of the disease. In 2017 we started to use the PET/CT imaging technique in a large vaccine evaluation study where it was used as a measure of vaccine efficacy.

Read more:

PET/CT imaging technique at BPRC

Research Areas

Tuberculosis

Local immunization strategy with BCG

Over the last 2 decades the TB group worked on major refinements of the monkey models. We now have a repetitive ultra-low dose challenge model in rhesus monkeys. This model is more similar to what happens in real life where people in endemic areas are frequently exposed to low doses of mycobacteria. We mimic this by repetitive exposing the animals to small amounts of tuberculosis bacteria. We validated this low dose model and used it to test the efficacy of local administration of BCG vaccine in the lung. We showed that this method was superior over the classical intradermal BCG immunization. More animals were protected from infection and less animals showed signs of TB disease.

Research Areas

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disabling disease in which the myelin of brain and spinal cord, the insulating layer around nerves, is attacked by the immune system. Genetic and environmental factors contribute to the disease, but the exact working mechanisms are still unknown. Animal models of human disease have an important role in the translation of scientific discoveries on disease mechanisms into new treatments. Our research group uses the EAE (experimentally-induced encephalomyelitis) model for MS in rhesus monkeys and marmosets to unravel the contribution of environmental factors to disease progression.

Translational MS research in primates

One of our PhD students successfully defended his thesis on translational multiple sclerosis research in monkeys. His research focused on disease mechanisms in the periphery and their effects in the brain. He found in archived EAE brain tissue from rhesus monkeys and marmosets that the mechanisms contributing to lesion development, namely oxidative stress and iron deposition, were very comparable between the marmoset MS model and disease in humans. In addition, he found that lesions do not only occur in the white matter, but also in the grey matter of the marmoset brain. Both the oxidative stress and iron changes as well as the grey matter lesions do not appear in most rodent models for MS and are therefore important features of the marmoset model.

Read more:

PhD awarded to Jordon Dunham at Groningen University

Comparable processes in the brains of a MS marmoset model and MS patients

Research Areas

Multiple Sclerosis

EBV-infected B-lymphocytes talk to T-lymphocytes

Epstein-Barr virus (EBV) is known to cause mononucleosis (Ziekte van Pfeiffer). Infection with EBV is also the strongest environmental risk factor of multiple sclerosis (MS), but a mechanistic explanation is still lacking. We have shown earlier that B-lymphocytes infected with an EBV-related herpes virus act as antigen-presenting cells in the marmoset EAE model and processes myelin different from non-infected cells. In 2017, we demonstrated that infection of B cells with EBV alters the expression of receptors and molecules and thereby alters the communication with T-lymphocytes. Altered markers on T-cells relate to migration to spleen and lymph nodes, pro-inflammatory responses, development and function. These results suggest that EBV does not need to be in the brain to play a role in MS.

Read more:

How do Epstein-Barr Virus (EBV) infected cells disrupt the immune system and thereby play a role in multiple sclerosis (MS)?

Research Areas

Comparative Genetics & Refinement

The immune system is orchestrated by many different genes. These genes can differ from individual to individual. This genetic variation within a population is called polymorphism. Polymorphism explains why some people are susceptible for a certain disease while others do not develop the disease. Hence, the diversity generated by these polymorphisms prevents the elimination of an entire population by one single pathogen.

Monkeys are genetically similar to people. Therefore, they are valuable in understanding polymorphisms, their role in the immune system and the consequences for the susceptibility for disease. This knowledge allows us to develop a whole new generation of treatments and medicines, that are specific for one individual instead of a whole population (personalized medicine).

One of the polymorphic gene systems is the Major Histocompatibility Complex (MHC). A set of genes that encodes for proteins that enable the immune system to detect and respond to pathogens, but also involved in eradicating cancer cells. In the Comparative Genetics and Refinement department, we investigate the MHC genes of monkey and ape species. We not only study our own animals, but also from other institutions and zoos. We use DNA-sequencing and other techniques, like fragment analyses on short tandem repeats (STR).

Research Areas

Comparative Genetics & Refinement

Does the selective sweep in the MHC region predate the speciation of the common chimpanzee and bonobo?

Chimpanzees are genetically the closest living relatives of humans. Chimpanzees are subdivided into common chimpanzees and bonobos (pygmy chimpanzees). Earlier, we showed that common chimpanzees have reduced variation in their MHC, compared to humans. This reduced MHC repertoire is the result of an ancient selective sweep, problably caused by an HIV-like virus. In 2017, we had the opportunity to investigate the DNA of 29 bonobos. We found that the MHC polymorphism was even more diminished than in the common chimpanzees. These results support that the ancient selective sweep in the MHC region, has predated the speciation of the two chimpanzee species.

Read more:

Limited MHC class I intron 2 repertoire variation in bonobos

Research Areas

Comparative Genetics & Refinement

Non-invasive technique for MHC typing

Genetic variation within a population is important for the survival of the species. It is therefore necessary that biological mechanisms are operational to maintain this variation. There are indications that mating choice and reproductive success is influenced by MHC and/or MHC-linked gene products. Therefore, non-invasive methods to type the MHC for conservation-biology of wild and captive primate populations are highly desired. This can be done by fragment analyses on STR. One of the primate MHC genes, named DRB, appears to have a highly divergent STR. The MHC-DRB shows copy number variation, which results in the presence of several different DRB genes on the chromosome. Recently, the STR length of DRB genes from silvery gibbons was validated, by using DNA from fecal samples.

Read more:

A quick and robust MHC typing method for free-ranging and captive primate species

Research Areas

Respiratory Viruses

Influenza (flu) is a contagious respiratory illness caused by influenza viruses. It can cause mild to severe illness. It is estimated that over 600,000 people have died of seasonal influenza in 2017. Many different influenza viruses are found around the globe and these viruses easily mutate to new virus variants.

Predicting the exact composition of the influenza vaccine is therefore complicated and sometimes results in a suboptimal vaccine protection. In addition, there is the constant threat of a new pandemic influenza virus. A 'new' virus that may be formed after recombination between bird-influenza viruses and pig-influenza viruses, and that is able cause serious disease humans. A scenario similar to the Spanish flu in 1918 which killed over 50 million people.

Ideally, an influenza vaccine would provide protection against a broad spectrum of seasonal influenza, as well as pandemic influenza viruses. However, to do so, new and improved vaccine-strategies are required. This involves improved vaccine production technologies as well as new vaccine concepts. Recently it has become clear that such protection requires not only so called broad neutralizing antibodies, but also other functions of the immune system. Already in 2015 we established influenza infection models in monkeys using particular influenza strains: H1N1 Mexico strain and the H1N1 California strain. In 2017, these models have been used to evaluate the protective capacity of several novel vaccine strategies.

Research Areas

Respiratory Viruses

Novel influenza vaccine evaluated in rhesus macaques

BPRC was partner in a collaborative European consortium: Educate Influenza Vaccine (EduFluVac). In this network we introduced a new vaccine concept. In 2017 we evaluated this concept in monkeys. The aim was to strengthen the induction of broadly neutralizing antibodies directed against parts of the influenza virus that are shared by many different viral variants. This was done by using a virus like particle expressing multiple varying influenza proteins.

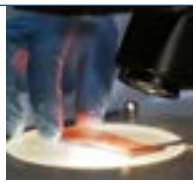
Read more:

EduFluVac

New *in vitro* assays

We have established and optimized several in vitro tests to analyze the anti-viral capacity of antibody responses. We used these tests to study antibodies after influenza vaccination or infection in monkeys. Especially antibody mediated cellular processes were studied. For instance killing of virally infected cells and the elimination of infected cells through phagocytosis. These assays will improve our understanding about what is required for achieving broad protection against influenza infection.

New PhD student influenza specific antibody responses



Protection from influenza infection relies on good antibody responses. With the employment of a new PhD student we will learn more from the influenza specific antibodies in the blood from vaccinated rhesus macaques.

Research Areas

HIV-AIDS

Last year 2 million people got infected with HIV, the virus that causes AIDS. Antiviral drugs can protect people from disease progression and prevents virus transmission. Over the years a lot of progress was made in providing anti-retroviral therapy to HIV infected people worldwide but still millions of new HIV infections occur each year. Stopping the HIV epidemic requires a more sustained solution, for instance a vaccine.

The development of an HIV vaccine is difficult because HIV is a 'smart' virus that developed many mechanisms to escape the immune system. The BPRC contributes to the battle against HIV by providing several (S)HIV models in monkeys. These models have learned us a lot about HIV infection and AIDS. Over the years many vaccines have been tested but none of them provide full protection against HIV infection. Thanks to monkey models we know much more about how 'smart' the virus really is and how it evades the immune system and vaccine induced immunity. But we still do not know enough to be able to develop an efficient vaccine that can be used to protect people world-wide.

In 2017 BPRC was partner in a large collaborative European consortium, the European HIV Vaccine Alliance (EHVA) sponsored by the EC under the H2020 program Read more. During this program we will evaluate several of new vaccines in monkeys.

HIV vaccine study in rhesus macaques leads to phase I study in humans

In 2017 nucleic acid-based vaccine strategies were tested. These new vaccines were combined with the already more established pox-vector and protein-based vaccination strategies. Vaccination of monkeys was successful. Based on this study one of the vaccines will be evaluated in a phase I clinical trial in people.

Research Areas
HIV-AIDS

New insights in HIV vaccines

BPRC staff co- published two scientific papers that describe the results from an HIV vaccine evaluation study performed in 2015. In this case a novel protein-based vaccine strategy was tested. Monkeys were immunized with a modified HIV envelope protein that represents an intermediate stage of virus when it binds to its target cell. This strategy specifically enhanced the induction of anti-viral antibody responses, which were more durable, and also resulted in other anti-viral mechanisms.

Read more:

Cross-Linking of a CD4-Mimetic Miniprotein with HIV-1 Env gp140 Alters Kinetics and Specificities of Antibody Responses against HIV-1 Env in Macaques

Pathogenic Events in a Nonhuman Primate Model of Oral Poliovirus Infection Leading to Paralytic Poliomyelitis

Research Areas

Mosquito-borne Diseases

Every year, more than 700 million people contract a mosquito-borne virus. The most well-known viruses are yellow fever virus, dengue virus, and Zika virus. Due to global warming and the growth of the human population the number of viral infections has dramatically increased. As there are no vaccines or antiviral compounds available for most of these viruses much research is needed. BPRC developed several animal infection models to investigate mosquito-borne flaviviruses.

A compound against dengue virus

In 2017, we started a collaboration with a European partner and performed a pharmacokinetics study in monkeys using a compound against dengue virus. This study was successfully performed. Based on the data obtained, an efficacy study is planned for 2018.

A new DNA-vaccine technology platform tested in rhesus macaques

BPRC is collaborating in the European funded project that aims to develop a dual-target rabies/flavivirus infectious DNA vaccine (RABYD-VAX). The RABYD-VAX DNA platform is based on a live-attenuated yellow fever virus. The first step in this project was to investigate if the live-attenuated yellow fever virus itself still works as a vaccine. Therefore, we performed a vaccination study in monkeys. Our study showed that the live-attenuated yellow fever virus is still able to induce an immune response. This is a good starting point. Our collaborators in the project are now modifying this vaccine so that it can also induce an immune response against rabies.

Read more:

RABYD-VAX

Research Areas

Mosquito-borne Diseases

Development of *in vitro* methods for mosquito-borne viruses

HONOURs is an international Innovative Training Network of 15 PhD students located throughout Europe. The program is funded by the European Commission to train Early Stage Researchers in all aspects of infectious outbreaks. BPRC takes part in this network. In 2017 a new PhD student started working on the development of in vitro methods to study pathological events after infection with mosquito-borne viruses.

Read more:

HONOURs

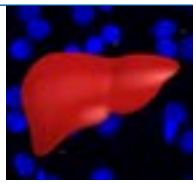
Research Areas

Malaria

Malaria is caused by the malaria parasite (Plasmodium) that enters the human body via a mosquito bite. Malaria kills almost half a million people each year. The focus of our malaria research activities in 2017 was on the use and optimization of the in vitro Plasmodium cynomolgi model.

We use this model to identify drugs that target dormant liver stage parasites (hypnozoites). P. cynomolgi mirrors the human malaria parasite P. vivax biology, including formation of hypnozoites, and infects rhesus monkeys. Because these parasite stages form a hidden reservoir in the population and complicate malaria control and elimination, much emphasis was put on drug-development for hypnozoites world-wide.

Cracking the code of dormant malaria parasites



Dormant forms of the malaria parasite can reactivate and cause new infections. This difficult to treat parasite stage has remained a mystery largely due to the lack of a culture system. The dormant malaria parasite stage is only present in humans and monkeys. The monkey malaria parasite offers more possibilities to find new drugs against this form of malaria. Together with partners from Singapore and Basel, using 'high-tech' technologies, we have built a comprehensive map of the genetic characteristics of this parasite form. This now offers new leads for the much-needed new medicines against this type of malaria.

Read more:

Breakthrough in malaria research

A comparative transcriptomic analysis of replicating and dormant liver stages of the relapsing malaria parasite Plasmodium cynomolgi.

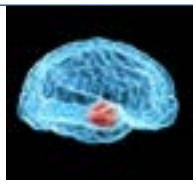
Research Areas

Parkinson's Disease

Parkinson's disease (PD) is, next to Alzheimer's disease, the most frequent age-related disease of the central nervous system. About 7 million people suffer from PD world-wide. At this moment there is no cure for PD.
PD is caused by the death of neurons in a part of the brain that controls movement. This damage results in the typical motoric symptoms, such as shaking, rigidity or slowness of movement. Other symptoms include sleep disturbance, depression and dementia.

BPRC has a well-characterized experimental model of PD in a monkey, the common marmoset. PD is induced by repeated injections of MPTP, which is converted into a toxic metabolite MMP+. MMP+ is selectively taken up in (dopaminergic) motor neurons and blocks the cell's energy production. Marmosets injected with MPTP develop characteristic non-motor (sleep disturbance) and motor symptoms.
PD research at BPRC is focused on understanding the processes that contributes to the pathology and clinical expression of the disease. Our model is used for the development of pharmaceutical and non-pharmaceutical therapies that stop the neurodegenerative process, suppress disease symptoms and prevent side effects of the current medications.

New treatment targets for Parkinson's disease in rhesus macaques



BPRC performed a transcriptomic study in monkeys. In this study we analyzed the gene expression in 15 anatomical brain regions of an aged rhesus monkey. The results of this work provides information about the pathological changes in the aging brains and potential new targets for treatment.

Read more:

Transcription start site profiling of 15 anatomical regions of the Macaca mulatta central nervous system

Research Areas

Parkinson's Disease

New compensatory mechanisms parkinsonian marmosets

BPRC has evaluated a new approach to target compensatory mechanisms by bypassing the damaged area in the brain. Increased sensorimotor rhythm (SMR) by neurofeedback technology activates a neurological compensatory pathway. SMR helps our brain to adjust to ever-changing conditions, including PD. In a standardized controlled study with parkinsonian marmosets we showed that non-invasive EEG-based SMR neurofeedback training results in a less progression of clinical signs and improves the therapeutic efficacy of the classical L-DOPA treatment. This indicates that SMR neurofeedback may allow lower dosages of L-DOPA limiting aversive side effects. This is an important indication of the therapeutic power of SMR neurofeedback in the treatment of PD.

Read more:

Sensorimotor rhythm neurofeedback as adjunct therapy for Parkinson's disease

Outreach

Biomedical research is not a goal. Our goal is to understand diseases and find a cure. We cannot do that alone. That is why we share our results and discuss them with other scientists. Together we know more and that brings us closer to the solution.

We (co-)authored

52 scientific publications in peer reviewed journals.

Find the complete list here.

we gave lectures

to train students

at Dutch universities and HBOs on possibilities and restrictions of working with monkeys in research.

We were visited by a BBC tv-crew for the

recording of a documentary

on the necessity of our research with monkeys. We showed them how we work.

We welcome visitors for

hosted tours and introduction lecture

on biomedical research.

We actively

feed our website

with relevant updates.

We organized

bachelor & master courses

for future scientists.

During

(inter)national meetings

we present and discuss our results.

We also organize

popular scientific lectures

in understandable Dutch for all BPRC staff.

We active participate in

annual meetings from patient organizations

to show them our results on 'their' disease.

We supervise and train

PhD, master & bachelor students.

After graduation they apply their knowledge elsewhere and contribute to science.

We organize lectures by

scientists from outside BPRC

to take lessons from their knowledge and experiences in other animal models or patients.

As partner in various research networks

our work is publicly available

via TransVac2, HONOURs, Vac2Vac, RABYD-VAX, and Bill and Melinda Gates Foundation CTVD.