BASR
2018

Biomedical Primate Research Centre
Annual Scientific Report 2018

Welcome

Join our journey through health research and alternatives

Biomedical Primate Research Centre

Contents

Monkey Research

- Explained -

Welcome to the 2018 annual scientific report from Biomedical Primate Research Centre (BPRC). 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, collaborations with (inter)national partners and (inter)national funding agencies. Together, this highlights our work as high standard and scientifically relevant.

On January 1st 2018 BPRC housed 1536 monkeys, 1082 rhesus macaques (*Macaca mulatta*), 260 cynomolgus monkeys (long-tailed macaques; *Macaca fascicularis*) and 194 common marmosets (*Callithrix jacchus*). On December 31st BPRC housed 1402 animals, 940 rhesus macaques, 286 long-tailed macaques and 176 common marmosets. In 2018 BPRC worked with 205 animals, 160 rhesus macaques and 45 common marmosets. These numbers were reported to the NVWA.

BPRC is committed to health research and alternatives. The development and implementation of the 3Rs, **R**efinement, **R**eduction and **R**eplacement are visible throughout BPRC. In this report you will find many examples of how refinement of animal models leads to a reduction of the number of animals.

Why do we still need animals for research?

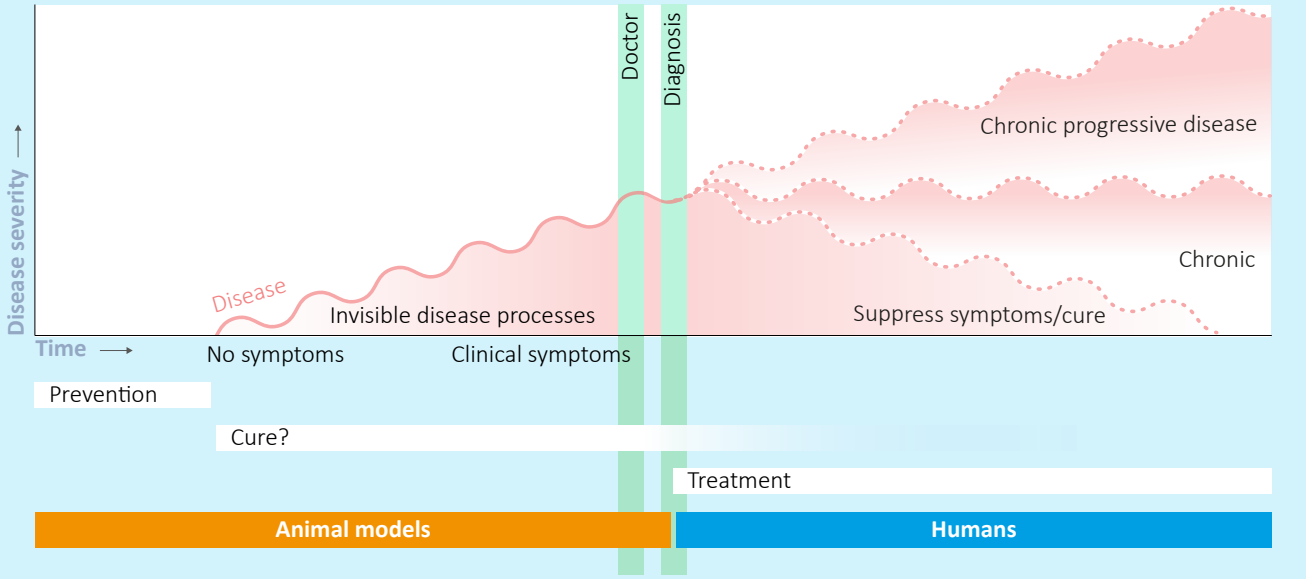
The European Commission concluded that the type of research conducted at BPRC cannot be done without life animals. That is because BPRC focuses on life threatening and/or debilitating diseases that affect millions of people. Diseases without cure or treatment because the complicated disease mechanisms are not yet fully understood.

Visualizing invisible disease processes

Because most (infectious) diseases start without clinical symptoms this type of research cannot be done in human volunteers. A patient only seeks medical help when he or she is suffering from disease symptoms. At that time the actual disease-process is already ongoing and caused damage to cells and/or organs. Therefore early and asymptomatic stages of a disease or infection are impossible to study in people. To 'visualize invisible' disease processes we depend on experimental animal models.

Monkey Research

- Explained -



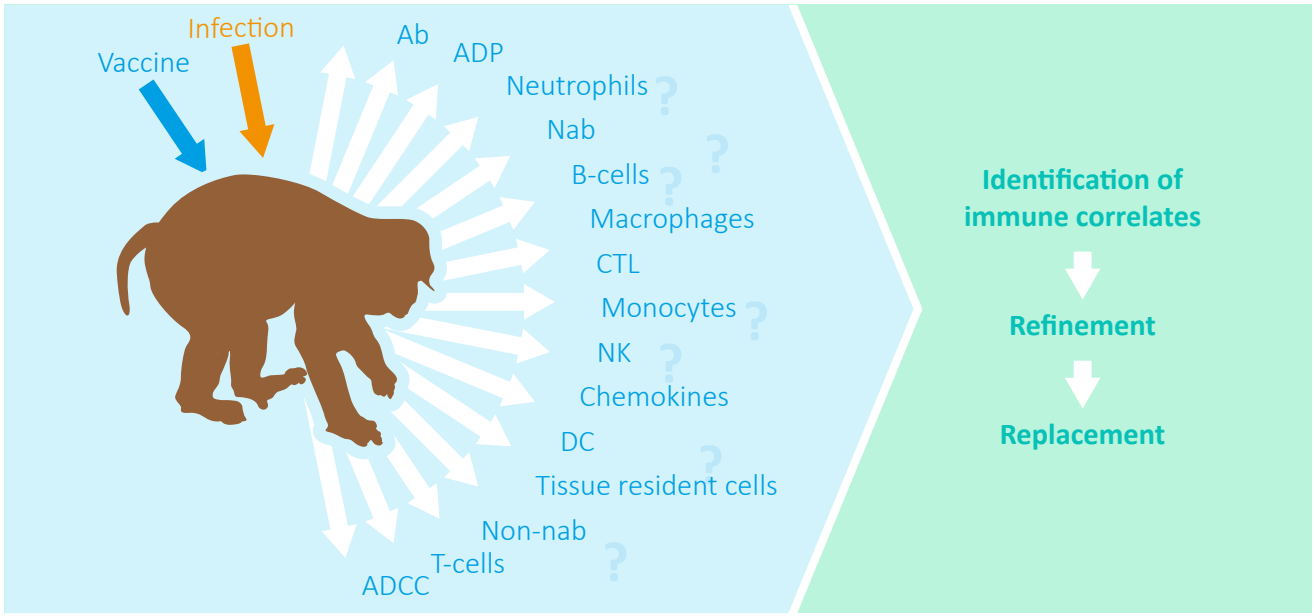
The X-axis represents the time and y-axis disease severity. A disease does typically not start with clinical symptoms. The onset is often without signs. But as time progresses the damage to cells and organs accumulate and cause clinically relevant disease. Depending on the disease this can take days to years. At that point patients go to a doctor and laboratory tests are needed to make a diagnosis. Only when diagnosis is made, proper treatment can start.
Most diseases have a so called point of no return. Before that the damage can be repaired, but when damage progresses beyond that point it results in irreversible (unrepairable) damage. In best case, the disease is diagnosed before the point of no return. Damage caused by the disease is reversible and treatment cures the disease. In case of a chronic disease, the disease cannot be cured. Drugs can help to suppress further disease progression but the damage is irreversible and drugs cannot undo the damage (MS). During a chronic progressive disease the symptoms are also irreversible and get worse. So far there are no drugs available to stop progression. Some infectious diseases are preventable by a vaccine (measles) or prophylactic drugs (malaria). Studying a disease and potential new medicines in people is only possible after the diagnosis of the disease. To study early events we rely on animal models that resemble the infection ir disease in humans. Understanding early events of a disease enables the identifying of the point of no return, hence decrease overall medical health care costs and increase quality of life. But also to develop animal-free alternative methods to evaluate new potential medicines.

Creating conditions for animal free alternatives

Unraveling disease processes is not only necessary to identify potential treatments but also to create the conditions for animal free-alternative methods to test vaccines or new treatments. Before you can even think about the development of animal-free methods you need to fully understand a disease and its critical events. In other words, you need to know exactly what you are looking for.

Monkey Research

- Explained -



In a prophylactic vaccine study, a vaccine is used to generate a pathogen-specific immune response. There is no specific lab test that can measure an immune response. The interplay between thousands of different molecules, including antibodies, cytokines, specific subsets of cells in the blood and chemokines, determine the quality and quantity of the immune response, and thus the protective effect of the vaccine. To test this, the animal is exposed the actual pathogen. The protective capacity of the vaccine is defined by the amount of virus, bacteria or parasite that can be detected after exposure. Little or no pathogen means the vaccine was successful.

Identification of (a combination of) molecule(s) that predict the effectiveness of the vaccine on forehand is a powerful refinement of an animal model. In the first place because evaluation of future new vaccine candidates does no longer require exposure to the pathogen itself to determine the effectiveness of a vaccine and therefore the discomfort of the animal is reduced. And second because it is the first step to the development of animal-free alternative techniques to evaluate potential new vaccine candidates.

To accelerate the transition towards a world without animal research, the Dutch Government stimulated BPRC to decrease the number animal experiments by forty percent by the year 2023. As there is currently no alternative method to replace the type of research performed at BPRC , this will have an impact on the development of vaccines and cures for influenza, aids, malaria, tuberculosis (TB), Dengue virus, multiple sclerosis, Parkinson's disease, and on the development of animal-free methods to evaluate future new vaccines and medicines.

Monkey Research

- Explained -

In this report we proudly present our contribution to science, the 3Rs and the development of animal-free alternatives.

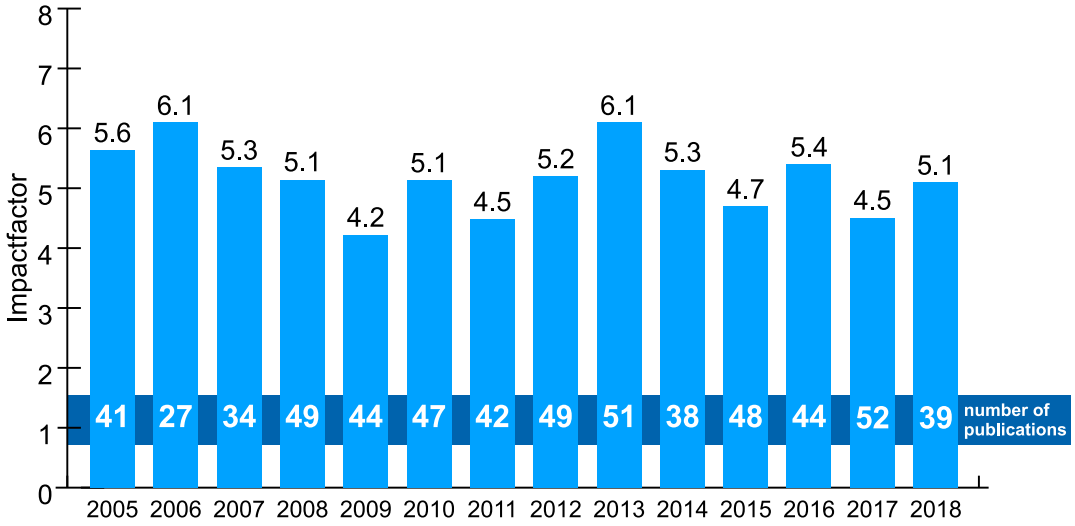
External links:

More information regarding animals in experiments is found at Stichting Informatie Dierproeven, European regulatory bodies (Directive 2010/63/EU), the Dutch law (Wet op de dierproeven). The Centrale Commissie Dierproeven (CCD) is the legal body in The Netherlands that is authorized to provide licenses. BPRC's accreditation by AAALAC International guarantees good institutional policies, animal husbandry and welfare, veterinary care at BPRC.

Message from the board

For BPRC, 2018 was another eventful year.

The quality of our scientific output continued to improve, and BPRC researchers published several important papers in high-ranking journals. The average impact factor of these scientific contributions rose from 4.5 to 5.1.



In fact, our research avenues stretch beyond public health. For example, certain research conducted by the Department of Comparative Genetics and Refinement highlights that BPRC is also active in the field of conservation biology. One paper that drew considerable attention concerns the genetic characterization of the immune system repertoire of the bonobo, a sister species of the common chimpanzee. It appears that some of the bonobo's immune system markers experienced a significant repertoire reduction that was likely caused by a malaria parasite.

Message from the board

Also in 2018, BPRC staff published several research papers in the field of the 3Rs, including refinement of veterinary methods. Other notable events were the invitation for one of our veterinarians to co-organize a meeting on Care, Use and Welfare of marmosets in Washington in 2018 and appointment of the head of the Animal Science Department as part-time Professor in “Welfare of Laboratory Animals” at Utrecht University.

The Supervisory Board and the Director congratulate the scientific and supporting staff on the obtained results, and we recommend reading this annual report.

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

Mr. J. Vrolijk
Chairman of the Supervisory Board

Our Financial Results

Foundation Biomedical Primate Research Centre (BPRC) closed the fiscal year 2018 with a zero result.

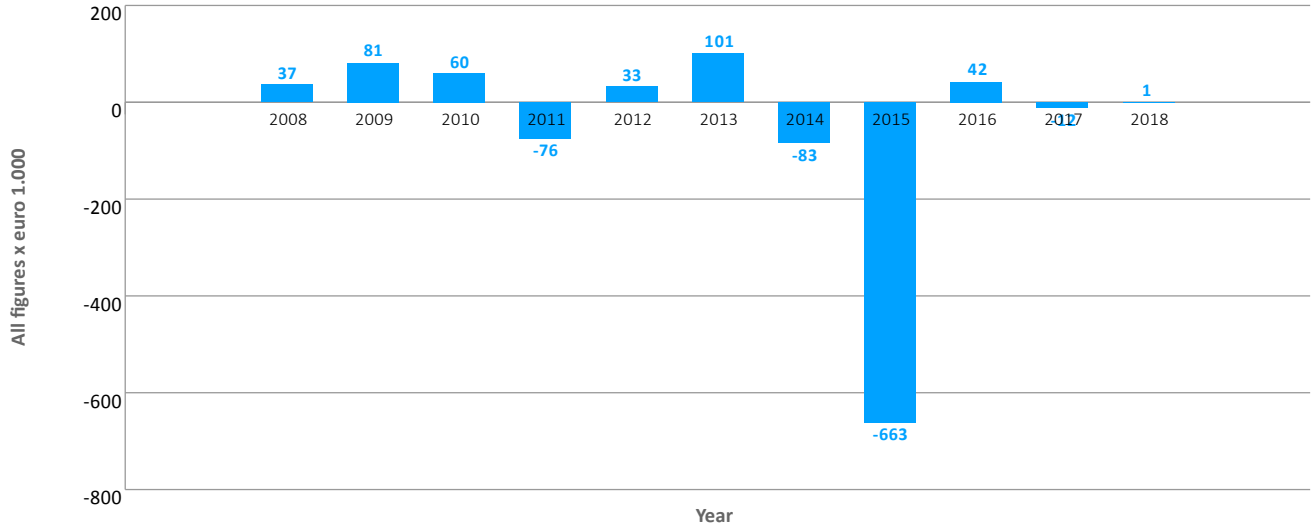
BPRC is a not for profit research institute that breeds its own laboratory animals and maintains its own research program. BPRC conducts biomedical / preclinical research for the identification and development of new medicines and vaccines for chronic and infectious diseases in humans.

BPRC also develops research methods that do not involve animal testing and operates under the highest (inter) national standards for animal welfare.

BPRC has many fixed costs in terms of animal facilities, security, high-quality equipment, feeds and cage enrichment, etc. The current workforce is around 110 FTEs and comprises scientists, veterinarians, pathologists, animal technicians, animal trainers and behavioural experts as well as technical, administrative and financial personnel.

Scientific institutes like BPRC are expensive and are directly or indirectly co-financed by the national governments.

Result development BPRC 2008-2018



Our Financial Results

PROFIT AND LOSS ACCOUNT

	2018 (K€)	2017 (K€)
Turnover projects (extern)	4.221	4.458
Turnover projects (subsidy)	7.081	7.079
Total turnover projects	11.302	11.537
Other excluding interest	1.217	1.102
	1.217	1.102
Total turnover	12.519	12.639
External direct project costs	678	912
Staff costs	8.004	7.782
Depreciation	492	396
Other operating charges	3.348	3.570
Total operating costs	12.522	12.660
Profit/loss on ordinary activities	3-	21-
Interest	4	9
Profit for the financial year	1	12-
Tax	-	-
Profit for the financial year after tax	1	12-

EFFECTIVE PERSONNEL

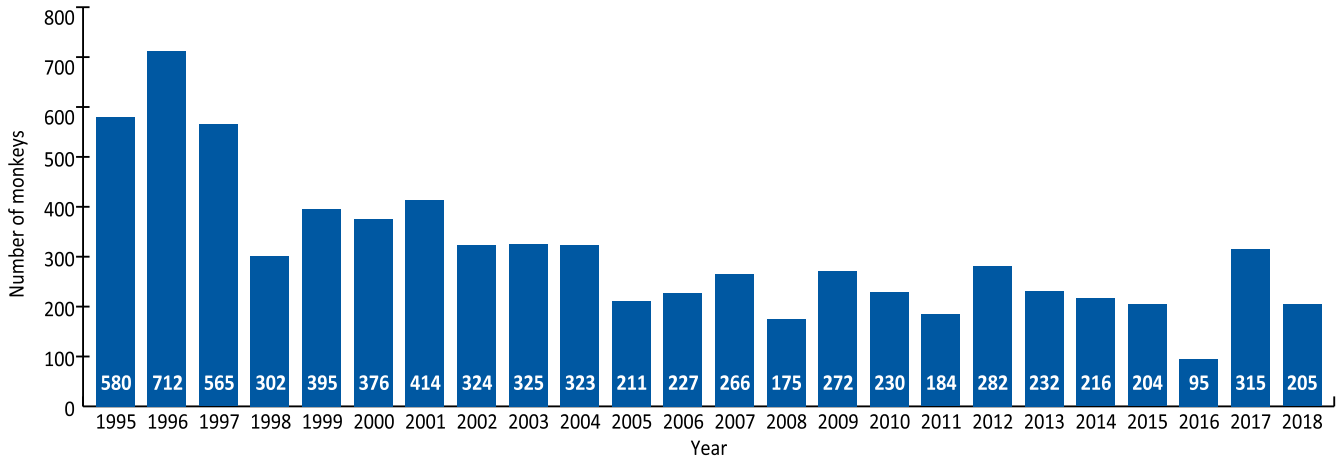
	2018		2017	
Service Departments	16,9	15%	14,9	14%
Animal Sience Department	46,0	41%	46,8	44%
Research	48,0	43%	44,8	42%
Total	110,9	100%	106,5	100%

BALANCE SHEET 31 DECEMBER

	2018 (K€)		2017 (K€)	
ASSETS				
FIXED ASSETS				
Buildings and structures	30.875		32.847	
Tangible fixed assets	1.796		1.668	
		32.671		34.515
CURRENT ASSETS				
STOCKS		44		47
DEBTORS DUE WITHIN ONE YEAR				
Work in progress	491		227	
Receivables from contracts	714		521	
Receivables tax	40		828	
Other receivables	248		182	
		1.493		1.758
Cash at bank and in hand		17.327		18.309
Total assets		51.535		54.629

	2018 (K€)		2017 (K€)	
LIABILITIES				
EQUITY				
Equity	4.759		1.715	
Revaluation reserve buildings	6.984		9.994	
Result current year	1		12-	
		11.744		11.697
PROVISIONS				
Primates	-		-	
Deferred tax liabilities	-		-	
(Flexibel) retirement	-		-	
Repairs buidings	2.770		2.847	
		2.770		2.847
LONG TERM DEBTS				
Bank	22.350		23.330	
Received in advance on assets	7.774		9.120	
		30.124		32.450
SHORT TERM DEBTS				
Received in advance on projects	2.048		2.508	
Received in advance on assets	272		361	
Received in advance subsidy	129		173	
Accounts Payable (TAX)	680		606	
(Flexibel) retirement	-		-	
Accounts Payable	1.417		1.470	
Commitment Bank	981		933	
Other liabilities	1.370		1.584	
		6.897		7.635
Total liabilities		51.535		54.629

Facts & figures



The number of monkeys we worked with over the years and the scientific achievements in 2018.

A total of

39 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 vaccines

on it's way.

New diagnostic tests for

difficult-to-treat-malaria

parasites.

Alternative way to mitigate

Parkinson's disease

symptoms.

New insights in what a

perfect flu vaccine

should do.

We are ready for

mosquito-borne virus

health issues.

1033 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

500 guests in 27 groups

on informative guided tours at BPRC.

We placed

37 updates on our website

in the newsfeed.

We train

7 PhD students

to write their PhD thesis.

We performed

>45,000 viral diagnostic tests

for zoos, sanctuaries and other clients.

We supervised

10 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

Monkeys are similar to humans. Not only on the outside but also on the inside. That is because monkeys are genetically related to us. Due to this evolutionary relationship monkeys sometimes are a good model to study human diseases. But only if there is no other way.

Working with monkeys brings a great responsibility. We are responsible for the well being of the animals in our colonies. We continuously seek to conduct research that does not involve animal testing in order to reduce the numbers of animals we work with. In the meantime we accommodate and look after our monkeys with the best possible care.

We do this using the principles of the 3Rs. Refinement, reduction and replacement. Refinement and reduction go hand in hand as Refinement of an animal model will lead to a Reduction of the number of animals per experimental group.

3Rs throughout BPRC

Refinement

- Improvement of animal welfare is a continuous process in our institute.
  BPRC staff take part in (inter)national training programs to remain their high standards and gain new insights.
- All animals are socially housed.
- Stress is not good. It affects animals in breeding groups and can even affect the results of an experiment. In order to avoid stress you need to identify stressful events. And for that you need unbiased, objective and reliable parameters to determine stress.
  - Measuring the cortisol levels in hair samples is a method that can provide stress information from an individual animal. By cutting a hair into smaller pieces you can relate the cortisol levels to potential stressful events.

Research Areas
Alternatives

  - We take pictures as an objective measure for alopecia. Alopecia (hairless body parts) can be a sign for acute stress. Caretakers are trained to detect this and to take pictures. Sometimes an animal experiences stress from hierarchy in their breeding group. If that is the case behavioral scientists are notified to monitor the breeding group and if possible take measures.
  - When animals are prepared for housing in an experimental setting they are introduced to a selected cagemate. We can use round the clock camera recordings to monitor their behavior in the absence of a caretaker. This avoids less-compatible pair-housed animals.
- Positive reinforcement training (PRT). We have trained 25 animal caretakers how to train their animals. They do this twice per week. With this training method we are able to perform certain biotechnical techniques without sedating the animal.
- All marmosets jump voluntarily on a scale. This way their body weight can be monitored 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.
- In 2017 an improved version of the ‘Welzijnsevaluaties’ was implemented.
- New features were introduced in our monkey database for the daily registration of each individual animal.
- All animals in experiments are observed at least twice a day. During this observation different parameters are ‘scored’. Normally an animal shows a broad variety of natural behaviors. In some models for (infectious) diseases the animal’s behavior changes. This is however a subjective parameter and changes are difficult to observe. Subtle changes during an experiment can provide crucial information. In this case we prefer to measure physical activity with telemetry. These devices register X-Y-Z coordinates of individual animals. If necessary it is also possible to measure body temperature, heartrate, blood pressure. This will lead to further refinement of our animal models.

Research Areas
Alternatives

Reduction

Optimizing and standardizing in vitro laboratory tests play an important role in the reduction of the animals we work with. Also in 2018 we have implemented new techniques. By using these new conditions, we aim at less variation in laboratory tests that will lead to smaller group sizes in our animal experiments.

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.

Statistics at BPRC
One of the hallmarks of good science is statistics. Not only at the end of a proof on concept study to determine whether an HIV-vaccine was successful but also during the design of the study. Therefore, good statistics is part of the 3Rs.

Statistics is often used to determine whether differences in study outcomes are (statistically) significant. This is normally done by rejecting or accepting the null hypothesis, where the null hypothesis states that treatment does not have a significant effect. To do so, the p-value is calculated. If the p-value is below 0.05, the chance that the study outcome arose by chance is smaller than 1 in 20. In that case, the null hypothesis is rejected, supporting the alternative hypothesis that the observed difference was due to the treatment.

But statistical testing is only informative if the study is properly designed. If group sizes are too small a real difference may not be detected and the study will not be informative. If group sizes are large differences will be detected, but at the cost of too many animals.

Research Areas
Alternatives

Therefore study design involves, amongst other things, also a so called “power calculation”. The number of animals per group is calculated based on the desired effect of the treatment on the primary outcome (e.g. diseased or not-diseased), the between-animal variation of the treatment effect and the desired power. The desired power is the chance that a real difference, if present, is detected. This is usually set at 80% (i.e. 80 out of 100 studies will yield significant results). Next to the power calculation, the study design also involves methodological topics like randomization of the animals (treatments are allocated by chance) and blinding of observers (treatment is not known). Next to the power analysis, a statistical analysis plan is written before the study is performed. Because monkey studies are often the last step before testing in humans, monkey studies should be designed, performed, analyzed and reported in a similar fashion as clinical trials in humans.

At BPRC statistics also involves analysis of observational data. Marmosets are usually born as twins or triplets. Yet, the mothers’ resources are often not sufficient to raise all three babies. Therefore triplet litters are not desirable. Based on observations made by our colony manager, we investigated whether marmoset mothers that were born as triplets are more likely to produce triplet litters. This proved to be true (*Bakker et al 2018 Am J Primatol*). The importance of this analysis is that we now can minimize the chance of triplet litters.
Read more >

PET-CT
Positron emission tomography–computed tomography (PET-CT) is a visualization technique that combines anatomic localization (x-ray) and functional imaging (nuclear medicine). In hospitals PET-CT is already widely used during the diagnosis and treatment of cancer. But quite recently PET-CT also found its way to biomedical research with animals.

PET-CT offers many advantages over traditional techniques. First, PET-CT is non-invasive. Results from blood tests, biopsies/swabs or cells washed out of the organ of interest can be indicative for infection, they are often poor indicators for actual disease manifestations. Biopsies only provide information of the tissue in the biopsy but often not of the entire organ. The combination of x-ray and specific radioactive probes allows screening of the

Research Areas
Alternatives

entire body. This minimizes the discomfort of the animals and provides you a much broader view.

In addition PET-CT offers the opportunity to visualize disease progression or therapeutic response over time (longitudinal). This is particularly relevant when critical organs need to be studied, like lungs or brains. PET-CT in combination with 18F-Fluorodeoxyglucose (FDG) as imaging agent is well-established and commonly used in both animals and humans. FDG visualizes the glucose metabolism in the body and shows increased signal in areas with inflammatory activity. This makes FDG PET-CT highly sensitive for detecting for instance tuberculosis and influenza lesions in the lungs.

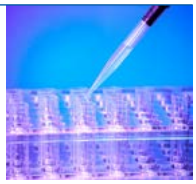
BPRC already started to use PET-CT in 2017. Initially only in our tuberculosis research but currently we are investigating the options to apply this state of the art technique also for other research programs. In the near future PET-CT will not only lead to new scientific insights but also increase the translational value of our animal models as PET-CT can also be applied to patients.
Read more >

Replacement

In 2009 BPRC-researchers developed an new in vitro assay to test drugs for it's 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 34 compounds. So far, BPRC tested 999 drugs with the animal-free assay.

Research Areas
Alternatives

3Rs Alternatives Unit BPRC



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 Replacement, Reduction and Refinement, 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.

Developing *in vitro* methods for the central nervous system

In the Western world, society is gradually aging and more and more 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 in such models are therefore highly relevant. Over the years we have successfully developed methods to study individual brain cells in test tubes. In 2018 we have made significant progress towards the development of in vitro methods that even better resemble non-activated cells tissue. In addition we have started an initiative to cultivate stem cells with the aim to generate 3D organoids, mini brains, in a dish.
Read more >

Research Areas
Alternatives

European initiatives: VAC2VAC and TRANSVAC2

Vaccines are the biggest success story of biomedical science. They have changed human life expectancy dramatically. Animals are not only used during the development phase of vaccines, but also during the production and quality control phase. We participate in European initiatives that aim to reduce animal use in both phases.

Vaccines are typically produced in batches. Every batch undergoes the same strict series of quality controls, involving many animal experiments, before it is released. The European VAC2VAC initiative 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, possibly circumventing animal testing. 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 2018. 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. The European TRANSVAC2 initiative is stimulating innovative vaccine approaches. We contribute by making our library of bioassays available to the European research community. In 2018 we have started research on the mechanisms that affect vaccine and adjuvant efficacy when immunization is done via the skin.

Research Areas
Alternatives

Developing an adjuvant without adverse effects

Adjuvants are formulations, which upon administration lead to non-specific immune stimulation. They are often used to stimulate immune responses directed against pathogens (for vaccination studies) or against components of the body itself (in animal models for human auto- immune diseases like multiple sclerosis). Some adjuvants are notorious for their adverse effects. Most notable is complete Freund's adjuvant (CFA), which causes inflammation of the skin accompanied by granuloma formation in non-human primates. It is however still being widely used in many animal species because of a lack of alternative. Using our bioassays, we have developed a new adjuvant in house, MiMyc. In 2018, MiMyc was tested in a small in vivo experiment and proved to be a potent adjuvant without causing adverse effects. If MiMyc can replace CFA in animal models for auto-immune diseases this would represent a considerable refinement. We aim to test this in the coming year.

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 behavior research but also to manage our breeding and experimental colonies. To improve our knowledge, we work together with a group of behavioral scientists from the University of Utrecht.

The behavior of female rhesus macaques to a new male

Newcomers in groups have to establish their social relationships with resident group members. The introduction of new, unfamiliar, males into captive monkey groups is necessary to prevent inbreeding but can also bear social risks. To minimize these risks, it is crucial to understand the social behavior accompanying male introductions. While the behavior of new males entering a group is generally understood, information on resident female behavior during introductions is lacking.

We studied female behavior towards immigrant males during introductions of three adult male rhesus macaques — each into a different captive group. All three males were successfully introduced; and respectively 100%, 92%, and 83% of the females tolerated the immigrant as a group-member at the end of the introductions. Older females started tolerating the male significantly faster than younger females, while no effect of female dominance rank, fertility, or the number of female coalitionary partners was found. During immigration, female aggression and submission towards the immigrant male, and male mating access decreased, while female affiliation toward the male increased.

In general, the process of tolerance and the changes in social behavior were similar between the introductions, indicating a general pattern in female behavior during male introductions.

Research Areas
Ethology

Based on these results, we suggest that female submission towards immigrant males may constitute a criterion to assess the risk of leaving a male in the group full-time. Overall, we conclude that female behavior to a new male is important and can provide valuable information about the immigration process during male introductions. Therefore, female behavior should not be overlooked.
Read more >

Research Areas

General Primate Biology & Welfare

Maintaining the health and stability of the monkeys in our self-sustainable breeding colonies requires dedication and expertise. This is a joint effort between BPRC's caregivers, veterinarian staff, behavioral scientists, laboratory staff and experts in genetics.

The monkeys live in social groups that recognize their natural behavior and social structure. Their living space is designed to give them a free choice to be in- or outside. This is not only beneficial to the animals, it also increases the translational value of our research. In contrast to most laboratory, animals do not live under so called SPF conditions. These artificial environment also has an effect on the development of the immune system. Our animals are naturally exposed to many everyday microbes. Animals in our colonies spend time outside, exposing themselves to pollen, bird droppings, insects and many more antigens, just like people do, and as a result they have a fully and naturally maturated immune system.

To keep our animals in good physical condition we monitor the animals for their general health and behavior. The expertise of our team is underlined by the fact that two of our staff members take place in the association of European Primate Veterinarians. In this international network veterinarians and other experts share information on general primate biology and welfare.
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 laboratorium performed over 45,000 diagnostic tests for external professionals.

Highlight in 2018:

Scientific publication on premedication on anaesthetic induction in common marmosets
Read more >

Research Areas

Tuberculosis

Tuberculosis (TB) is a bacterial infection that causes lung disease. TB is currently the deadliest infectious disease in the world. In 2017 1.6 million died of TB. In addition, over 10 million people fell ill from TB and approximately 25% of the world population is latently infected with TB. In Western countries TB patients are treated with a cocktail of antibiotics. However, anti-microbial drug resistance in TB is increasing, which makes it harder to treat. Overall, a growing number of TB infected people cannot be treated and die of the disease. Prevention by vaccination is the only means to break the cycle of TB transmission and infection.
Read more >

BPRC uses TB models in the rhesus monkey and the cynomolgus monkey to get a better insight in how the disease develops and to evaluate new treatments of TB. The two models represent two different disease manifestations. TB in rhesus monkeys develops as a progressive active form of the disease, while infection of cynomolgus monkeys can develop as a latent disease.

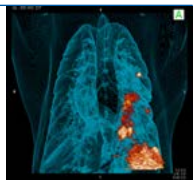
Local administration of BCG-vaccine superior to classical skin immunization

For the evaluation of new vaccine candidates, we work with the rhesus monkey. Over the last 2 decades the TB group has been working to refine the rhesus monkey model by challenging the animals with smaller amounts of tuberculosis bacteria. Last year we reported on the development of a repetitive limiting dose challenge model in the rhesus monkey (read more; article and commentary). This model more closely represents what happens in real life where people in endemic areas are repeatedly challenged with low doses of mycobacteria. This year we used the repetitive limiting dose infection to compare the efficacy of two immunization routes of the BCG-vaccine. We observed that local immunization in the lung was superior to classical immunization in the skin. Some animals were even protected from infection. Moreover, in the animals that were

Research Areas
Tuberculosis

not fully protected, a reduced bacterial burden and disease was observed. Currently, we are investigating the adaptive and innate immune responses in the animals. The results from these experiments are expected to be published in 2019.

PET/CT to visualize successful treatment



Active TB infection poses a major public health risk. Patients are contagious and spread bacteria by coughing. Therefore, patients with active TB are treated with antimicrobial drugs. However, bacterial resistance is on the rise. Long-term use of antimicrobial drugs is the most important cause of the development of drug resistance and should be avoided. However, this calls for new therapeutic strategies. In 2018 we successfully visualized the reduction of TB disease after treatment of an established infection. Longitudinal PET/CTs imaging were used during a combination therapy of 2 commonly used antibiotics. We will further develop PET/CT to evaluate therapeutic strategies, which can be vaccination or host directed therapy (HDT). In this way we aim to hope to improve anti-microbial drug regimens and identify strategies that can help in the fight against drug resistant TB.

Research Areas

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic progressive disease. During MS the insulating layer around the nerves of the brain and spinal cord, the myelin sheath, is attacked and destroyed by the immune system. Genetic and environmental factors contribute to the disease, but the exact working mechanisms are still unknown. Currently, there are no drugs available to cure MS. Animal models can help to understand early events and to translate these into potential new treatments. For this, BPRC uses the EAE (experimentally-induced encephalomyelitis) model.

EBV-infected B-lymphocytes talk to T-lymphocytes

Epstein-Barr virus (EBV) is the virus that causes mononucleosis (Ziekte van Pfeiffer). Infection with EBV is also the strongest environmental risk factor of MS, but a mechanistic explanation is still lacking. Earlier we showed that B-lymphocytes infected with an EBV-related herpes virus processes myelin different from non-infected cells. Here we collected evidence that citrullination of myelin can shift the disease pathogenesis towards neurodegeneration.
Read more >

Research Areas

Multiple Sclerosis

How changing diet reduced MS-like disease in marmoset monkeys

At BPRC we use the experimentally-induced encephalomyelitis (EAE) model to study MS in humans. In this model marmoset sensitized with recombinant human myelin oligodendrocyte glycoprotein in IFA develop clinically evident EAE. After the introduction of a new supplement to the diet of our marmosets, the development of EAE decreased from 100 to 65%. To investigate if there was a relationship between the diet and the induction of EAE, a study was performed with twin siblings. One of the twin siblings was reverted to the original diet while the other was not. In the reverted siblings 100% disease prevalence was observed, whereas in siblings remaining on the new diet the EAE prevalence was 75%. Spinal cord demyelination, a classical hallmark of the disease, was significantly lower in new-diet monkeys than in monkeys reverted to the original diet. Systematic typing of the marmoset gut microbiota using 16S rRNA sequencing demonstrated a unique, Bifidobacteria-dominated composition, which changed after disease induction. RNA-sequencing revealed reduced apoptosis and enhanced myelination in the brain. Our data show dietary intervention exerts positive effects on EAE-related parameters in multiple compartments of the marmoset's gut-immune-CNS axis.

Read more >

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. Polymorphisms explain 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.

The Major Histocompatibility Complex (MHC) and killer cell immunoglobulin-like receptor (KIR) system are examples of polymorphic gene systems. A successful immune response is multifactorial, and depends on the cooperation between the KIR and MHC system. In general, the MHC system is involved in discriminating between self and non-self and thus the recognition of invading pathogens while the KIR system may be seen as fine tuning and serves as a correction mechanism for the MHC system. KIR genes are involved in the immune defense to viruses and cancer cells.

Monkeys are genetically similar to people. Understanding genetic polymorphisms in monkeys, and their role in the immune system, teaches us much about the functional immune defense in humans. This is particularly important in the development of a whole new generation of medicines, the so-called personalized medicines.

In the Comparative Genetics and Refinement department, we investigate MHC and KIR genes from different monkey and ape species. For this, we use DNA-sequencing and other techniques, like fragment analyses on short tandem repeats (STR). We not only study the DNA from animals from our own breeding colonies but also DNA samples from other institutions and zoos.

Research Areas

Comparative Genetics & Refinement

West-African chimpanzees show limited MHC class II gene variation

Genetic diversity is detrimental for the survival of a species. When a 'new' pathogen invades the population genetic diversity increases the chance that some of the individuals survive and prevent the species from extinction. If all the individuals within a population have the same genetic background and these genes are not capable of generating an immune response against the pathogen, all individuals will die and the species will become extinct. Genetic diversity can prevent this and the survivors can reproduce to generate a new population. In evolutionary terms this is called a selective sweep. In ancient history chimpanzees went through a selective sweep. As a result they have a reduced variation in their MHC class I genes . BPRC has a collection of blood cell samples from western chimpanzees. Recently, we used these samples to investigate five genes that belong to the MHC class II region. We observed that the repertoire of variants of these class II genes was limited. However, the number of different combinations of the five genes (haplotypes) was high. These results indicate that-after the selective sweep- variation within the class II gene-region was generated by crossing-over processes. Our results underline the plasticity of the primate's immune system to remain genetically diverse. This mechanism can decrease the vulnerability of the species and therefore increase the chance of survival of the species in case of another new pathogen invades the population.
Read more >

Research Areas

Comparative Genetics & Refinement

Does the MHC confer protection against malaria in bonobos?

Malaria parasites are widespread among wild chimpanzees and gorillas. Yet, malaria is rare in the smaller cousin of the common chimpanzee, the bonobo. Immunological factors explaining the near absence of malaria parasites in bonobos are not yet understood. In humans the class I variants HLA-B*53 and B*78 are associated with protection from malaria. In 2018, we observed functionally similar MHC class I molecules in bonobos. Our data suggest that the MHC class I repertoire in bonobo was positively selected to control malaria infection.

Read more >

MHC class I variation in olive baboons

The olive baboon (*Papio anubis, Paan*) belongs to the Old-World monkeys, and is used as a model species in various fields of biomedical research, like neuroscience and transplantation. Little is known about the olive baboon MHC class I genes. We combined two fast and accurate molecular typing methods to unravel this complex gene system and found a high number of baboon MHC class I A (Paan-A) and B (Paan-B) alleles. Similar to other old-world monkey species, such as the rhesus macaque, the alleles show different transcription levels, and the combination and number of genes (haplotypes) vary. Moreover, we showed that particular olive baboon MHC class I alleles share a specific part (epitope) with human and rhesus macaque MHC class I alleles, that could be recognized by KIRs expressed on Natural Killer cells. Future binding experiments between MHC and KIR molecules in baboons or other old-world monkey species are needed to elucidate if their molecular interactions are similar as observed for the HLA-KIR interaction in humans.

Research Areas

Comparative Genetics & Refinement

Killer cell immunoglobulin-like receptor (KIR) polymorphism, a comparison between humans and rhesus macaques

Natural Killer cells express a diverse repertoire of killer cell immunoglobulin-like receptors (KIRs) on their cell surface. KIRs can either activate or inhibit NK cell function and are thereby important regulators of an immune responses. The KIR genes display abundant copy number variation as well as high levels of polymorphism, and as a result, it is challenging to characterize this structurally dynamic region. We used a Pacific Bioscience's Sequel platform to sequence the KIR transcriptome of both human and rhesus macaque families. This approach allowed the identification of human and rhesus macaque KIR haplotypes, of which the latter contained several novel Mamu-KIR alleles. In addition, this method identified hybrid genes that are the result of chromosomal recombination. Using the same approach, extensive alternative splicing has been demonstrated for the human and rhesus macaque KIR transcripts, which diversifies the KIR repertoire even more. Overall, these results illustrate the plasticity of the KIR gene system in primates, and provides a better understanding and interpretation of KIR associated diseases, as well as the immune reactivity in transplantation and reproductive biology.

Read more > and more >

Research Areas

Respiratory Viruses

Influenza (flu) is a contagious respiratory disease caused by influenza viruses. It can cause mild to severe illness. Every year over half a million people die of seasonal influenza. Many different influenza viruses are found around the globe and these viruses easily mutate to new virus variants.

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 in 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, current influenza vaccines afford only limited protection against seasonal as well as pandemic influenza. Therefore, new and improved vaccine-strategies are required. This involves new vaccine concepts as well as improved vaccine production technologies.

At BPRC we use influenza infection models in monkeys to evaluate the protective capacity of several novel vaccine strategies.

Research Areas

Respiratory Viruses

Experimental animal models for universal influenza vaccines

BPRC was partner in a collaborative European consortium: Educate Influenza Vaccine (EduFluVac). As part of this network a workshop was organized. During this workshop a diversity of models to evaluate universal influenza vaccines were discussed. The program covered well-established and publicly accepted animal models, newly developed animal models as well as *ex-vivo* approaches and human models. The audience concluded that, depending on vaccine approach and the type of immune response, different models are required. As safety is the main concern for transition to clinical development, influenza vaccine associated enhancement of disease was specifically emphasized. An efficient animal model to evaluate this aspect of safety still needs to be identified. Working with animal models requires ethical compliance and consideration of the 3R principles. Development of alternative approaches such as *ex-vivo* techniques is progressing but is still at an early stage. These methods are not yet suitable for broader application for vaccine evaluation. The human challenge is the ultimate model to assess influenza vaccines. However, this model is expensive and not largely applicable. The currently used pre-clinical models are not yet specifically focused on studying unique aspects of a universal influenza vaccine. Further collaboration, communication and effective networking are needed for success to establish harmonized and standardized pre-clinical models for evaluation of new influenza vaccines.
Read more >

Research Areas

Respiratory Viruses

Needle-free influenza vaccine protects rhesus macaques against H1N1 influenza

The production of conventional influenza vaccines is a complicated and time consuming process. By contrast DNA vaccines can be rapidly produced and offers tailor-made flexibility to efficiently counter newly emerging influenza virus strains. However, a drawback of DNA vaccines is their generally low immunogenicity in non-human primates and humans. Norwegian scientists have developed a novel DNA influenza vaccine strategy that induced good immune responses in ferrets and pigs. BPRC evaluated this vaccine in rhesus macaques. The vaccine, a DNA vaccine encoding for a bivalent fusion protein that targets influenza virus hemagglutinin (HA) to Mamu class II molecules, was intradermally administered by pain- and needle-free jet injections. The vaccine induced neutralizing antibodies and antigen-specific T cells and protected against a challenge with influenza virus. This type of needle free DNA vaccination may become an effective way to rapidly and efficiently protect people to emerging seasonal or pandemic influenza virus strains. The information of this study will be published in 2019.

Research Areas

Respiratory Viruses

Mini-hemagglutinin vaccination induces cross-reactive antibodies in pre-exposed NHP that protect mice against lethal influenza challenge

By the age of 6 years, virtually all people have detectable influenza-specific antibodies. However, these antibodies are only effective if the next influenza infection occurs with a virus variant that strongly resembles the previous one. In the light of yearly vaccinations to seasonal influenza it is important to know if antibody responses can be broadened by vaccination.

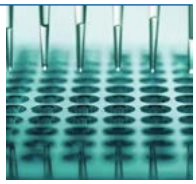
In 2015 we conducted a study in collaboration with Crucell Vaccine Institute. This work was published in Science (*Impagliazzo, A. et al. Science, 2015*) and described a successful influenza vaccine approach with the so-called 'mini-HA' in our monkeys. In 2017 blood samples from these animals were used to investigate the protective capacity of the antibodies in the blood of the animals. This was done by adoptive transfer in mice. Mice that were inoculated with antibodies from monkeys that received the influenza vaccine after they were exposed to influenza virus were better protected from influenza infection compared to mice that received antibodies from animals that were only exposed to the virus. This study suggests yearly vaccination may broaden the influenza-specific humoral immune responses in humans.

Read more >

Research Areas

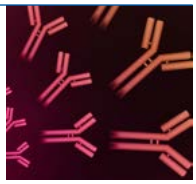
Respiratory Viruses

New in vitro assays



At BPRC we are constantly developing and optimizing in vitro laboratory assays to analyze the anti-viral immunity. We use these tests to study immune responses after influenza vaccination or infection in monkeys.
In 2018 the focus was on the implementation of new assays that visualize antibody mediated cellular processes in our animals. 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.

PhD student influenza specific antibody responses



Protection from influenza infection relies on good antibody responses. In collaboration with the Amsterdam Medical Centre we are currently training a PhD student to study the plasticity of antibody producing B-cells. For this project we use *in vitro* models and blood samples from previously vaccinated rhesus macaques. The results of the project will lead to better understanding of antibodies after influenza-vaccination.

Research Areas
HIV-AIDS

Hiv is the sexually transmitted virus that causes AIDS. Treatment with antiretroviral drugs not only prevents AIDS in the patient, it also prevents transmission of the virus to others. Therefore antiviral drugs play an important role in the battle against HIV, but it is not enough to stop the pandemic. Last year 2 million people got infected with HIV and a vaccine would be of great benefit.

BPRC contributes to this field with several (S)HIV models in monkeys. We use these models for proof of concept studies for new vaccine candidates. Over the years BPRC evaluated many vaccines but so far none provided full protection against HIV infection. Thanks to monkey models we know much more about how 'smart' the virus is, and how it evades the immune system and escapes from vaccine induced immunity. Classical vaccine strategies do not suffice and more complicated vaccine strategies are required.

New insights in HIV vaccines

The European HIV Alliance (EHVA) is a multidisciplinary network supported by the EU. It comprises of 39 academic and industrial research partners, one of which is BPRC. One of the aims is to develop an effective HIV vaccine and bring that to the clinic. Latest insight is that a, so called, prime-boost vaccine strategy has the best chance to provide protection from HIV infection. To determine the best priming strategy, BPRC performed a proof of principle study in monkeys. The study compared an HIV-encoding RNA vaccine that replicates only in dividing cells, an HIV-encoding replicon that replicates in all cells and an mRNA/TriMix vaccine. The results are now being evaluated within the network.

In parallel, other partners within the network are working on the optimal boosting strategy. In a later stage, a combination study will be needed in rhesus monkeys to determine the best prime-boost combination. The best candidate will be moved forward to the clinic. Moreover, the data from the network partners will be used to identify immune correlates of control of HIV replication following immunological intervention.
Read more >

Research Areas

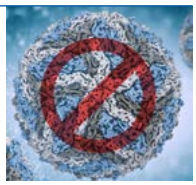
Mosquito-borne Diseases

Dengue virus, West Nile virus, Rift Valley fever virus and Zika virus are mosquito-borne viruses that cause a transient infection in people. In most people the infection is transient and without clinically relevant illness. Approximately 1% of the patients suffer from complications. Nowadays, over 700 million people get infected with a mosquito-borne virus each year. Due to the growth of the human population and global warming this number is expected to increase dramatically over the next decades.

So far vaccines are only available for Dengue virus and Yellow fever virus but these vaccines have severe limitations as are not advised for the ones that run the highest risk for complications, namely children, older people and those people with an impaired immune system.

BPRC developed several infection models to investigate mosquito-borne viruses. In 2018 these models were mainly used for proof of concept-studies for vaccines and antiviral medicines.

An antiviral medicine dengue virus



There are four different types of dengue viruses. A first infection results in lifelong protection against infection with the same serotype. However if the second infection occurs with another serotype the patient has in increased chance to develop disease. This phenomenom is called antibody dependent enhancement (ADE). Severe dengue disease is a potentially deadly complication due to plasma leakage, fluid accumulation, respiratory distress, severe bleedings, or organ impairment. Every year half a million patients require hospitalization and about 20,000 people die of severe dengue.

In collaboration with a European partner we performed a preclinical study to evaluate an antiviral medicine. The results of this proof of concept-study were promising. The treated animals had less virus in their blood compared to the non-treated animals. But more research is needed before this medicine can go to the clinic.

Research Areas

Mosquito-borne Diseases

A new DNA-vaccine technology platform tested in rhesus macaques

Yellow fever is a vaccine-preventable mosquito-borne virus infection. However, the commercially available vaccines are so called life-attenuated vaccines and cannot be used in children and older people. In addition, the production of these vaccines is time consuming, requires batch-to-batch evaluation and the distribution requires a so called cold chain. This hampers a rapid response in case of an outbreak. On top of that, recent outbreaks caused a severe vaccine shortage.

New generation vaccines may overcome these problems. DNA vaccines are safe, can be rapidly produced and do not require a cold chain. However, not all DNA vaccines are effective.

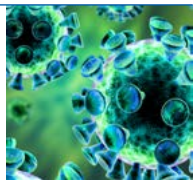
BPRC is collaborating in a consortium funded by the EU. The project aims to develop a dual-target rabies/flavivirus DNA vaccine. The first step in this project was to investigate if the DNA-vaccine that encodes for a live-attenuated yellow fever virus still works as a vaccine. To test this, we performed a proof of concept study in monkeys. Our study showed that the DNA vaccine was indeed capable of inducing an immune response. Yet, not in all animals. Currently our collaborators in the project are modifying this DNA-vaccine so that it can also induce an immune response against rabies.

Read more >

Research Areas

Mosquito-borne Diseases

Rift Valley fever virus



Rift Valley fever virus (RVFV) is transmitted by mosquitoes. It primarily affects animals but can also infect humans. In cattle and sheep the virus causes abortions. Most human RVFV infections manifest as a transient, flu-like illness. A small percentage of humans develop encephalitis or hemorrhagic fever, which may be fatal. Currently Rift Valley Fever virus outbreaks are restricted to African counties but it was shown that also the most prevalent European mosquito (*Culex pipiens*) is also capable of transmitting the virus. An outbreak of Rift Valley Fever virus in The Netherlands will cause dramatic direct and indirect economic damage. As partner in Castellum, a collaborative consortium that includes the Dutch National Institute for Public Health and the Environment of the Ministry of Health, Welfare and Sports, the Wageningen Bioveterinary Research group was asked to develop a veterinary vaccine against Rift Valley Fever virus. As part of this program BPRC performed a proof of concept-study in monkeys to investigate if the 4S vaccine was safe for (non-human) primate species. Our study showed no adverse effects in common marmosets and there was no evidence for virus replication. The vaccine will be further developed by the Wageningen Bioveterinary Research group.

Read more >

Research Areas

Mosquito-borne Diseases

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

HONOURs is an international Innovative Training Network funded by the European Commission. The aim of the project is to train 15 PhD students in all aspects involved in host switching pathogens, infectious outbreaks and zoonosis. Preparedness requires expertise in many areas. The Early Stage Researchers are therefore located at academia and research institutes throughout Europe that together cover the entire field of outbreak-control. BPRC is involved as expert on modeling infectious diseases in non-human primates. In this program we focus on the development of *in vitro* methods to evaluate pathological events after infection with mosquito-borne viruses.

As part of HONOURS, BPRC organized a 4-day course for all 15 students. During this course presentations were given from BPRC staff members, as well as guest speakers from the Erasmus University Medical Center in Rotterdam. The presentations focused on different non-human primate models for infectious diseases and neurological disorders, but also dealt with biosafety, study design, ethics, genetics, ethology, animal training and colony management. In addition, a one-day workshop was included with various laboratory techniques that are widely used in our virus research projects.
Read more >

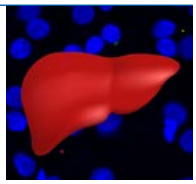
Research Areas
Malaria

There are different types of malaria parasites but for humans *Plasmodium falciparum* and *Plasmodium vivax* are the most relevant ones. *P. falciparum* because it causes severe disease and *P. vivax* because this parasite can remain silently present in the liver.

These 'dormant' parasites ("hypnozoites") are invisible to the immune system and while they are sleeping they do not cause disease. However, there is always the risk that these parasites wake up and cause a new malaria infection. Current antimalaria drugs are not effective in preventing these malaria relapses. Therefore, hypnozoites form a hidden reservoir in the population, and they complicate malaria control and elimination. Worldwide much emphasis is put on drug-development for hypnozoites.

In humans it is not possible to study hypnozoites, therefore we use the *Plasmodium cynomolgi* model. *P. cynomolgi* mirrors the human malaria parasite *P. vivax* biology, including the formation of hypnozoites, but it infects rhesus monkeys.

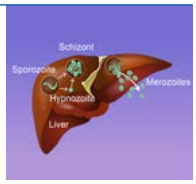
Cracking the code of dormant malaria parasites



The *P. cynomolgi* model offers possibilities to find new drugs against the dormant liver stage malaria. Together with partners from Singapore and Basel, we have increased our knowledge of the genetic characteristics of this parasite form. Using state of the art technologies, we have shown that the parasite, when deep asleep, still has some activities, albeit at a low level. This information will be used to identify potential targets for new medicines to prevent malaria relapse in people that carry hypnozoites.
Read more >

Research Areas
Malaria

Detecting the presence of dormant malaria parasites



Currently there is no diagnostic test to detect hypnozoites, the dormant malaria parasites in the liver. If, and when, new medicines are available to wipe out hypnozoites such a diagnostic test is necessary to identify patients that require treatment. Together with Japanese colleagues, we are pioneering the development of a diagnostic test for hypnozoites. For this we use our hypnozoite *in vitro* culture model. The test is based on subtle changes in specific molecules from the host cell after infection with a hypnozoite. The results of initial small-scale tests are promising and will be followed up in 2019 with larger scale analyses.
Read more >

Research Areas

Parkinson's Disease

With approximately 7 million people suffering from Parkinson's disease (PD) world-wide it is one of the most frequent age-related diseases of the central nervous system. 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. At this moment there is no cure for PD.

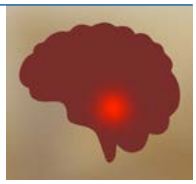
Because most PD-patients only seek medical attention after the disease has progressed, early event of the disease cannot be studied in humans. BPRC has a well-characterized experimental model of PD in a monkey, the common marmoset. PD is induced by repeated injections of MPTP, which is converted into 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.

Research Areas

Parkinson's Disease

Compensation by the Red Nucleus may explain why primates can develop stable Parkinson's disease



BPRC identified a new target to manage Parkinsonian symptoms. This approach focuses on a part of the brain called the "red nucleus". This red nucleus controls movement in quadrupedal animals (animals that walk on four legs, like rodents and cats), and it also regulates the crawling movement in babies until other areas of the brain then take over. It is known that the red nucleus in PD is enlarged compared to non-PD people. Presumably because the red nucleus gets activated to compensate for affected parts of the brain.

Our researchers examined whether the same phenomenon could be observed in monkey models of PD. Their findings showed that animals with a larger red nucleus displayed fewer Parkinson's symptoms than animals with a smaller red nucleus. In addition, stimulation of this compensatory pathway seemed to increase the size of the red nucleus even more. The study also focused on a part of the red nucleus that mainly occurs in humans and primates. Though a different part of the red nucleus is active in quadrupeds, it is striking to note that these animals can spontaneously recover from PD symptoms, whereas this is not observed in primates. This is yet another indication that the red nucleus may be very important.

The information from this study is currently being prepared for publication and will be published in 2019.

Research Areas

Parkinson's Disease

Refinement of the MPTP model for the induction of Parkinson's disease in the marmoset monkey

The MPTP-model in common marmoset monkey is frequently used for PD research. However, there is still a debate about the level of discomfort in this model.

BPRC has performed a meta-analysis to identify the most optimal induction protocol minimizing discomfort for the monkey. This resulted in a refinement of our MPTP marmoset model by lowering the dosage and increasing the interval of MPTP administration. The new approach minimizes the interference of direct effects of the toxin MPTP on clinical signs that may have an impact on the animal and the outcome of the results. It also reduces the discomfort for the animal as the progression of the clinical features develop more slowly over time, which also mimicks the human counterpart of PD.

Finetuning of the MPTP-induction protocol may, therefore, improve the well-being of the animal and development of rational, effective treatments for the multifactorial pathogenic mechanisms of PD.

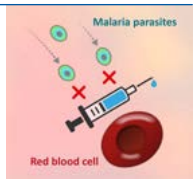
Read more >

Research Areas

Protein Core Facility

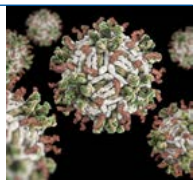
BPRC is often a collaborative partner to evaluate new vaccine candidates. Yet, we also have our own pipeline for vaccine development. The scientists at BPRC have many years of experience in vaccine development.

Malaria vaccine



PfAMA1, the protein vaccine against the malaria parasite *Plasmodium falciparum* was developed at BPRC's protein core facility. AMA1 plays a key role in the entry of the parasite into red blood cells and therefore AMA1 is a good vaccine candidate. After optimizing vaccine design, expression and purification procedures the vaccine was used in a proof of concept study in monkeys. After an extended vaccination procedure PfAMA1 provided partial protection against the malaria disease. However, in people the vaccine did not suffice. Combining PfAMA1 with another vaccine candidate may overcome this in the future.

Virus like particles vaccine platform



Virus like particles (VLPs) are molecules that resemble viruses but VLPs do not contain genetic material, and thus non-infectious. VLPs are capable of activating the immune system and generate a virus specific immune response. Therefore VLPs are sometimes used as a vaccine. The vaccine that is currently used to protect women from cervical cancer caused by HPV is also based in virus like particle technique.

In line with this, BPRC's protein core facility designed VLPs for Usutu virus and Zika virus. Both vaccine candidates are in early stage of development. The envelope proteins were produced by recombinant techniques, purified and biochemically prepared to generate VLP's. *In vitro* experiments showed that both Zika as well as Usutu VLPs bind Zika and Usutu specific antibodies, respectively. Both VLPs will be further evaluated for immunogenicity and their potential as human vaccines.

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

39 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 De Buitendienst 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 & PhD 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.