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Biomedical Primate Research Centre

# Leading the way in research

Adjacent Digital Politics Ltd highlights the excellent research work taking place in the Netherlands and the Ministry of Education, Culture and Science…

The Netherlands are at the top of their game when it comes to research and development (R&D). In 2009 the country spent over €10bn in the area, with almost 10,000 people getting involved.[1]

Research and Development in the country is supported by three main sources of funding: companies, the government and foreign entities. The government equates to 37% of the funding with companies making up 49%. The Ministry of Education, Culture and Science is responsible for promoting, funding and supporting research projects within the Netherlands.

Working together with universities and organisations such as the Netherlands Organisation for Scientific Research (NWO), the Ministry distribute necessary budgets to universities in order for them to excel in a certain specialism and market their knowledge.

"In the Netherlands we have an excellent knowledge infrastructure in which this is done at a large scale by world class researchers," explains Babs van den Bergh, Director Research and Policy at the Ministry of Education, Culture and Science.

"It is important to maintain this situation and to develop our knowledge further and to pass it on to the new generation of inquisitive people. Only in this way will we be assured of those clever people in the Netherlands who can help solving the big world issues and keeping our economy running."[2]

The Ministry of Education, Culture and Science are seeing a growth in the number of public-private partnerships, with around €90m being redistributed in the field of science and research. The government is supporting research and providing incentive funding to encourage international cooperation in this area, because high quality research is integral to solving social problems and boosting the economy.

Innovations and new products are essential for a nation to grow and gain further insights into areas of medical science that are important to tackle health challenges such cancer, HIV/Aids and Malaria.

"Innovations, new products and other services are essential. However, really innovative insights are not the result of goal-oriented search – after all then you already know what you are looking for," said Van den Bergh.

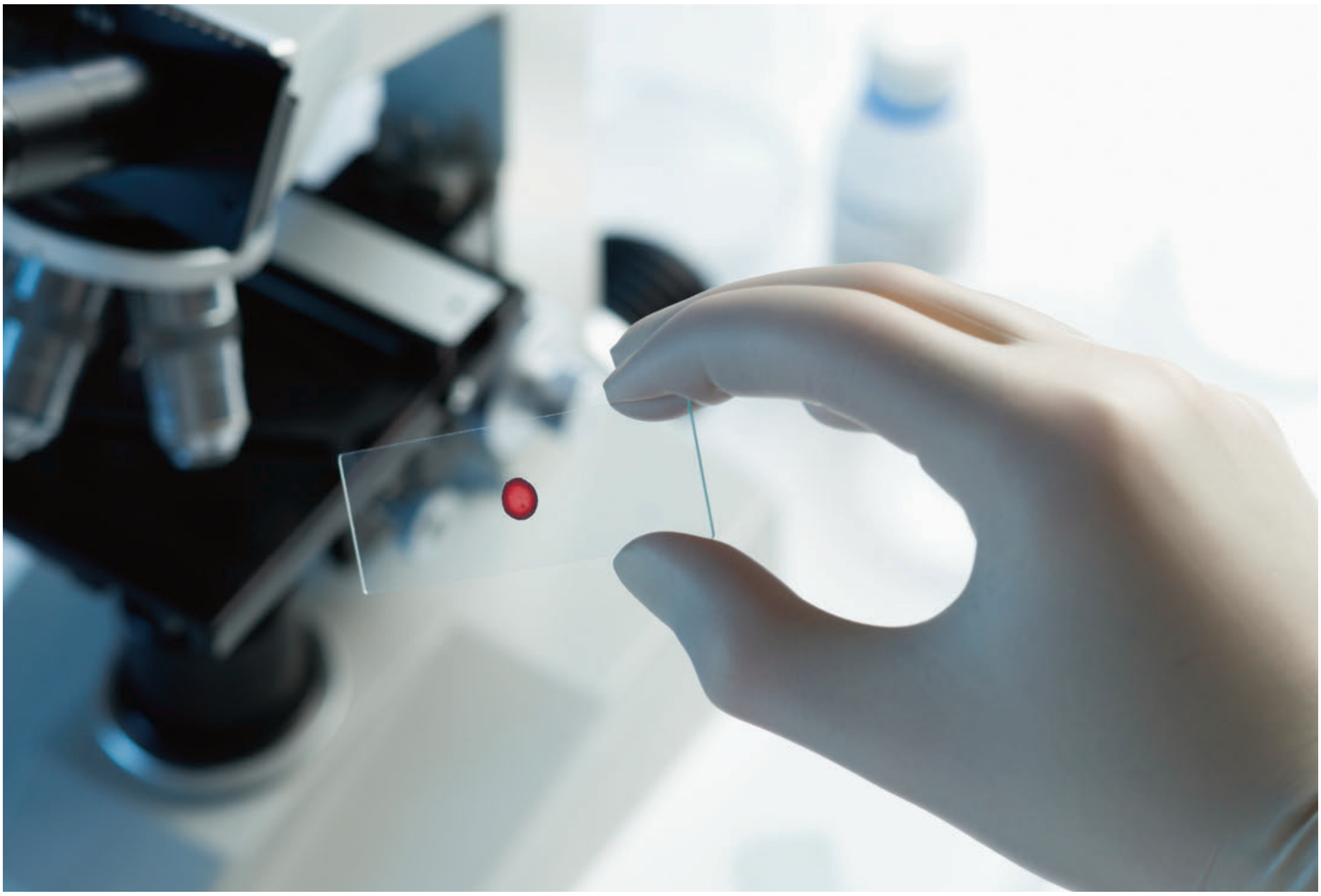
"At OBW we think along with the scientists. We help them with organising the infrastructure, streamlining international projects, for example by taking seats on the boards of European organisations, or by co-reading new research agendas."[3]

There are many areas of research that are conducted within the Netherlands, explaining to some extent why they are top of the league when it comes to R&D.

**Case study – Biomedical Research**

Biomedical research is used to deal with health issues that cause misery to people's lives, resulting in a desperate need for effective medicines.

Life threatening diseases such as HIV, Aids, Tuberculosis and Malaria, require effective drugs and vaccines to help



treat, protect and prevent deaths from occurring. Through biomedical research, knowledge is gained in order to tackle what is seen as major health challenges around the world.

For such critical research, and to help understand the human body and the way complex diseases affect it, it is key for basic research to be undertaken to protect human health and the environment. Due to the similarities between primates and humans – this makes primates crucial for medical research and understanding the impact that exposure to chemicals and drugs have on the human body.

Approximately 12 million animals are used each year for scientific research and procedures in the EU. Among these are 10,000 non-human primates (nhp's), which are mainly monkeys and apes. Using primates in medical research has led to some important findings in biology and medicine. To conduct and understand such complex research (such as brain research) and infectious diseases, primates play a unique role. The reason for this is due to their immune system being very similar to that of humans. Primates are usually the species that match humans more closely in terms of how drugs affect them and tests on other species are simply not adequate.

In the Netherlands, medical research using primates is conducted by the Biomedical Primate Research Centre (BPRC) – which is at the forefront of biomedical research. This lead in the field is helping to develop new medicines.

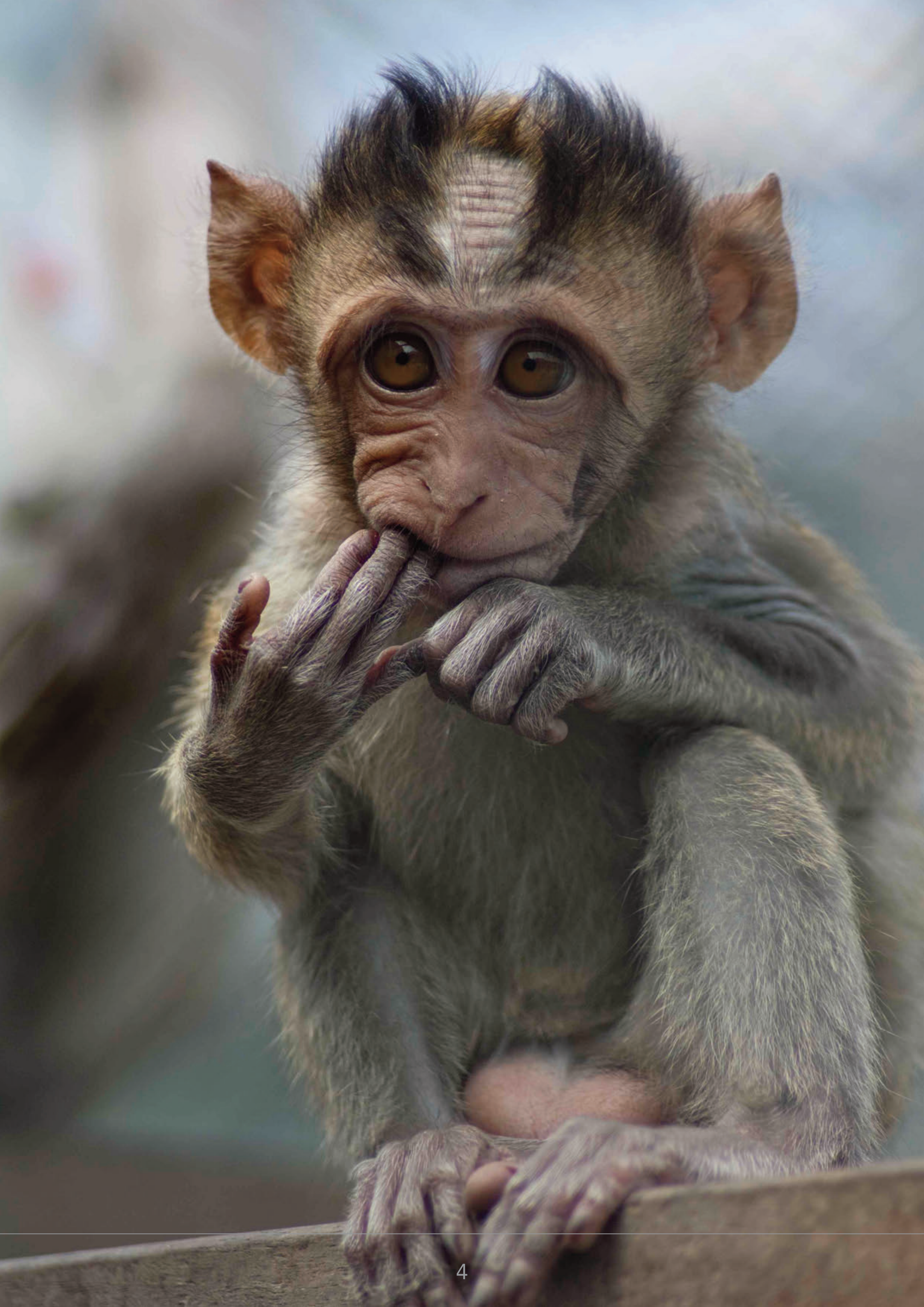
The BPRC works to develop medicines to treat serious and deadly human diseases and therefore has an important but difficult mission – to continue research to help improve human health.

References

[1] http://www.bladerbrochure.nl/brochure/code/63VR5q7W6v6A24oQqeieS6UVQrkins

[2] (ibid)

[3] (ibid)



# Non-human primates and health research

Animal models play an essential role in the development of new medicines, vaccines and therapies for the benefit of human health. Within animal models for biomedical research, non-human primates belong to a special group. The use of these highly developed animals needs specific attention. The use of animals in biomedical research raises concern by the general public, and when non-human primates are used this is even more so. Non-human primates are social animals and given their highly developed social behaviour and skills, the use of non-human primates in biomedical research raises ethical and practical issues. However, in the light of the current state of scientific knowledge, the use of non-human primates in scientific procedures is still necessary.

Within the new European Directive 63/2010, that regulates the use of animals for scientific purposes, there is special attention for the use of non-human primates. They can only be used for biomedical research, and only in areas that are essential for human health and where no alternative models are available (including other animal models such as rodents). Their use is only permitted for specific areas of basic research concerning preservation of the species, or for biomedical research on potentially life-threatening and debilitating diseases in humans. The use of great apes (i.e. chimpanzees), is not allowed for biomedical research in several European countries . The EU Directive specifically states that great apes are only used under very specific conditions, and that the Member state claiming such a need must provide information necessary for the Commission to take a decision. In Europe, there is no chimpanzee colony available for this purpose.

The use of non-human primates is very limited and amounts to only approximately 0.1% of the total number of animals used for research in Europe. The majority of non-human primates used in research are imported from licensed breeding centres, mainly from Asia, and has several problems. Although care is taken that these animals are not captured from the wild, it is regularly only the first generation animals born in captivity that are used. Within Europe, a feasibility study for the development of self-sustaining colonies and provision of sufficient animals for the European biomedical programs will be performed.

Transport of non-human primates by air is getting very difficult due to both strict regulations and the refusal of many carriers to transport non-human primates destined for biomedical research. Pressure from animal right activists to stop animal transport is getting stronger making transport of live animals difficult. Furthermore, long-distance travel is very stressful for the animals, and import of animals requires strict quarantine procedures at the host institute. In order to minimise the need to import animals, European self-sustaining breeding centres should be used (similar to those in the United States). Many of the non-human primates for research are bred at the National Primate Research Centres, and this provides an opportunity to further increase animal welfare. Such self-sustaining colonies prevent much of the transport stress and insure that all animals are bred and cared for following the local rules and guidelines. Currently, there are several non-human primate breeding colonies in the Netherlands, Germany, France and the UK, with by far the largest being the BPRC in the Netherlands and the DPZ in Germany. Although such breeding colonies are costly

compared to those in Asia, the advantages outweigh the disadvantages, and further development of these centres in Europe would guarantee optimal care for animals. They are developed according to the most recent knowledge on animal welfare and provide housing in social structures that are as natural as possible. Other strong advantages are the guarantee of strict breeding programs, easy provision of genetic background, medical history of the animals, and dedicated training and enrichment programs for the animals throughout their life. Over-all, this would benefit both research and animal welfare. Currently, the number of self-sustaining primate colonies for biomedical research in Europe that can provide animals for the scientific community, is too limited to provide all non-human primates needed for research.

Monkeys are divided into 2 groups: the Old World monkeys, i.e. monkeys from Asia and Africa; and the New World monkeys from the America's. The most widely used non-human primates in biomedical research are Old World monkeys, mainly rhesus macaques and cynomolgus macaques, and in specific cases baboons or vervet monkeys are used. In Europe, no great apes are used in biomedical research. The most widely used species of New World monkeys is the common marmoset.

Each animal model used to study human disease has its own pro's and con's. It becomes clear that with development of our knowledge and understanding of more personalised medicine, small animal models do not always provide the relevant information. Other, more sophisticated and/or more closely related animal models that reflect the situation better in humans are needed. One of the most important reasons to use non-human primates in biomedical research is their close phylogenetic relationship with man. We share many physiological, behavioural and genetic characteristics and susceptibilities for various diseases. The genetic make-up of man and monkeys can be similar for more than 90%, depending on the species, and  the comparability is very high for several important systems, including the immune system. Therefore, biomedical research in non-human primates can contribute to our understanding of these diseases and fundamental biological phenomena and are important in the development of new therapies, drugs and vaccines.

Non-human primates are instrumental for the promotion of human health and play a critical role in the advancement of various areas in the medical field. Examples where non-human primates have played an essential role are: the development of bone-marrow transplantation and transplantation protocols; the development of vaccines against infectious diseases like polio; and the increase in understanding of important diseases like yellow fever and Hepatitis. Non-human primate models have been essential in the identification of causative agents of infectious diseases, such as: typhoid fever, mumps, yellow fever, and SARS, and contribute to our general knowledge of processes underlying normal situations and disease processes.

The use of animal models to study human diseases have advantages in various situations. Fundamental properties of diseases can be studied using well-defined models, extensive sampling, and new prophylactic and therapeutic treatments can be studied in such models to provide proof-of-concept before advancing into clinical trials, thus limiting risk and time. In selected diseases, non-human primates provide the most suited animal model for such studies.

Non-human primates are susceptible to many infectious diseases that also affect humans, and thus provide interesting animal models for studying new therapies and vaccines. One example where they play an essential role is in HIV research. Originally studied in chimpanzees – the only species beside man that can be infected with HIV, albeit without developing AIDS – the natural primate counterpart of HIV, i.e. simian immunodeficiency virus (SIV) is used to mimic the disease in macaques. SIV infection in macaques results in a disease comparable to AIDS in man. Rhesus macaques provide an important animal model for the study of disease and development of therapeutics and vaccines against HIV and AIDS. Although it is often argued that these models still did not result in a validated, safe and reliable vaccine against HIV in man, these models have been essential for the development of new strategies to protect HIV-infected people from developing AIDS.

Many of the current therapies would not have been possible without the research that has been performed in macaques. Moreover, these models in macaques have been instrumental to our understanding of disease development, and recent studies have now provided essential information on the early phases of the disease, something that would not be possible to do in man.

Although HIV research is one of the most generally known topics to study in non-human primates, monkeys are also used in research on other viral diseases. The recent fear of influenza pandemics after the H1N1 outbreak and the more avian strains that infect man directly has resulted in a resurgance in flu research. Macaques are used as an experimental model to study pathogenesis and immunology of influenza virus. These animals develop immune responses and disease symptoms comparable to that in humans and viral replication can be detected in the nasal area and respiratory tract. No adaptation of the virus is required and in contrast to the often used ferret model, a wide array of immunological tools to study specifics in pathogenesis is in place. Therefore, macaques are used to study important questions in influenza pathogenesis and to test new vaccines against influenza strains from human and avian origin.

Besides influenza, our fear of new diseases and the rapid spreading of diseases due to climate change and the increased mobility of man, for example, has led to an increase in research on emerging infectious diseases. Examples of such diseases are West Nile virus infection, Rift Valley fever, SARS and Chikungunya (outbreaks of these diseases have been seen over recent years). The rapid spreading of West Nile virus in the USA and the occurrence of this disease in the south of Europe indicates the importance in the rapid development of tools to combat these diseases. Non-human primates are used to study specific details of these diseases because of their natural susceptibility and the comparability of disease development, which is not possible in the small animal models.

Non-human primates are also used in non-viral infectious research. Like humans, non-human primates are susceptible to infections with the bacterium causing tuberculosis. This is most common in macaques, who develop a disease resembling human tuberculosis. Unfortunately, the current vaccine is not very effective in adults and new vaccines are urgently needed. Worldwide, tuberculosis is still one of the main causes of death in humans. The recent occurrence of multi-drug resistant and extreme multi-drug resistant strains of Mycobacterium tuberculosis, the causative agent of tuberculosis, stresses the importance to learn more about the pathogenesis and develop new and effective therapies or vaccines. This non-human primate model is used for fundamental research aimed at understanding disease processes in tuberculosis and correlates protection as well as the development of new vaccines.

They contribute to rational down-selection of TB vaccine candidates to progress to advanced clinical studies, which is costly and time-consuming. Another recent development is the model for whooping cough in baboons. Although vaccines exist, a steady increase in whooping cough cases has been observed and the current vaccines are not sufficient to control this. The often used animal models, mostly mice, do not meet the need to replicate the full spectrum of disease. In contrast, baboons have been observed showing the prolonged cough and transmissibility of the causative agent, Bordetella pertussis and offer a much more reliable model to study this disease. Interestingly, rhesus macaques do not mimic this disease, most likely due to their higher body temperature, demonstrating that it is essential to validate each disease model.

Parasites form a different and difficult group of pathogens with respect to vaccine development. In order to develop vaccines for parasites still more research is required because parasitic diseases are extremely challenging. One of the most serious parasitic diseases is malaria. The two major species are Plasmodium falciparum, which causes the deadly malaria tropica, and Plasmodium vivax, leading to high morbidity in large parts of the world. There are no natural models to study these malaria parasites directly, although Aotus monkeys can be infected with blood stages. However, these animals are a protected species and only very limited numbers are available. More importantly, there are various primate malaria parasites that are closely related to human malaria parasites. Since metabolism and immune system in macaques are highly similar to that in humans, macaque models in malaria research closely resembles the situation in man. Using these macaque models, researchers are gaining knowledge on malaria biology, and are beginning to overcome the major obstacles in malaria vaccine development. Based on research in non-human primates several malaria vaccines are currently tested in humans.

Due to the comparable immune systems between non-human primates, especially macaques, and humans, they are often used to analyse the immune responses and safety of new vaccines before they are applied in man. Moreover, these non-human primate models provide controlled conditions to study and unravel complex interactions between pathogens and the host, which increases our understanding of disease development and provides a knowledge base for rationalised design and acceleration of new vaccines and therapies.

Non-human primates are also used to study many non-infectious diseases affecting humans. Various diseases with an underlying immune-related disorder are studied using non-human primates. Multiple sclerosis (MS) and rheumatoid arthritis (RA) are both auto-immune diseases that affect the life of many people. Specific non-human primate models provide the means to study various aspects of these diseases that cannot be studied in man. Although many animal models used to study these diseases concern rodents, it is increasingly clear that the predictive value of these models is limited. Especially with respect to the more personalised medicine approaches and the development of medication that affects very specific targets in the human body, better and more predictive models are essential. In various cases, non-human primates can offer such models. Experimental models for MS and RA have been developed in non-human primates, especially macaques and common marmosets, to provide the bridge between rodents and man. These models are providing insight on the immunological mechanisms underlying the development of MS and RA, and are instrumental in the development of new therapies.

The way in which the brains of non-human primates and humans are organised is highly similar. The use of non-human primates in brain research is important to understand the functioning of the brain, and provides knowledge on functioning under normal conditions and in brain-related diseases. Like humans, common marmosets are susceptible to an agent that induces Parkinson's Disease like symptoms in both species. Because marmosets, can handle complex behavioural tasks that enable testing cognitive functions in Parkinson's Disease, this model is used to study disease therapies and neuroprotective methods. Unlike rodents, marmosets with induced Parkinson's Disease show a wide range of Parkinsonian behaviour that is also present in humans, which makes this primate model very valuable to develop new interventions therapies. Research using brains obtained from deceased macaques and great apes in comparison with humans is used to study evolutionary aspects of aging for example. Studies have identified interesting aspects of potentially involved mechanisms.

In auto-immune diseases like MS, and neurodegenerative disease like Alzheimers and Parkinson's Disease, non-human primate models are used to study new treatment. A recent and exiting development is the use of stem cells. The potential of such cells as therapy is currently studied in relevant non-human primate models. This will certainly result in new insights with respect to disease development and the development of curative or preventive therapies.

Another field of neuroscience where monkeys play an essential role is in the development of new ways to deal with prosthetics. It has been shown that by specific research and mapping of brain areas, new devices have been developed that could be steered by the monkey solely using its 'thoughts'. This opens the pathway to new applications of neuro-based steering of prosthetics by patients. Monkeys are used to map the brain in more detail and to study a number of aspects involved in brain development.

Non-human primates are also used to understand more about various aspects of human evolution. Research using brains of deceased macaques and great apes, and then compared with human brains, is used to study evolutionary aspects of aging, and recent studies have shown interesting mechanisms that might be involved. Comparisons of several components of the immune systems are used to learn more about evolution. Non-human primates are also used to study social evolution by looking at aspects of cooperation, bonding, altruism and sexual behaviour. Comparison of these aspects between man and their closest relatives lead to interesting insights into our own behaviour.

These examples of the use of non-human primates demonstrate that they provide important models for various areas in biomedical research. Because of their close phylogenetic relation with humans, non-human primate models have been, and are still, providing essential knowledge in our struggle against life-threatening and debilitating diseases.

One of the promising advances has been the sequencing of the genome of various non-human primate species that are used in biomedical research. This knowledge of the genome and genes involved in immune regulation together with the developed animal models in the various disease areas will increase our understanding of the mechanisms involved in these diseases and/or protection against them.

The use of non-human primates in research is a continuous matter of debate. Although many scientists are convinced that they are useful in several areas of research to answer specific questions, we also have the obligation to always be able to justify this use for the general public. Furthermore, if we decide to use non-human primates in biomedical research, this also comes with the obligation to take optimal care for these highly developed animals and to recognise their specific needs with respect to housing and care. It is essential that these animals are housed and treated in such a way that meets their natural behavioural, environmental and social needs as much as possible. During the past decades many things have changed for the better, and under the new Directive, all animals will be socially housed in large cages. Furthermore, the animals need to be mentally stimulated during the day, for example, giving them the opportunity to search for food. For all primates engaged in biomedical research, enrichment programmes have to be in place and carried out carefully. To prevent side effects of enrichment, e.g. overfeeding, specific guidelines for enrichment have been developed. More recent developments also include training protocols for the animals – to cooperate with procedures voluntarily in order to prevent stress and sedation as much as possible. Non-human primates react very well to positive reinforcement training (PRT). Besides learning to cooperate with certain procedures, PRT also provides enrichment. It is strongly advocated that all facilities working with non-human primates also include PRT training. This addition will benefit both the animals and research.

It is clear that non-human primates have been and still are essential in the advancement of biomedical research. However, we have to realise that each individual has its own intrinsic value and if we decide to use these animals for our own benefit, we also have the obligation to treat these animals in the best way we can.

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