The next generation of neuropharmaceutical drugs

NEUROBASIC PHARMAPHENOMICS
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PHARMAPHENOMICS
Introduction

In front of you lies a splendid book about the groundbreaking results that have been achieved within the NeuroBasic LSH-FES consortium. LSH stands for ‘Life Sciences & Health’, or rather the application of life sciences to the benefit of our health, and FES for the ‘Fund for Economic Structure Enhancement’, financed by the so-called natural gas profits. NeuroBasic started its activities in 2010 after the Dutch government’s approval of a joint proposal. This proposal was submitted by a combination of many partners – including small and large businesses, multinationals, academic and medical research groups, patient organisations, and the ministries of Health, Welfare & Sport, Education, Culture & Science, and Economic Affairs. The FES grant was used to achieve a public-private partnership: for every single euro subsidised by the government, the partners also invested one euro. After six years of hard work, the results can be directly applied in the treatment of patients or used for research that is closely linked to patients. The consortium has hereby proved that it deployed the research funds to contribute to the improvement of our national public health and to boost economic activity in the Netherlands. A vast number of these results are presented in this book. The most recent developments in this exciting field will astonish you time and time again. I therefore trust that you will greatly enjoy reading this book!

Herman Verheij
LSH-FES SECTOR COORDINATOR

NeuroBasic PharmaPhenomics has picked up where NeuroBSIK MousePhenomics, which was also funded by FES money, left off. MousePhenomics yielded us standardised methods for measuring brain diseases by way of a mouse model. Ahead of us, the challenge was in using this extremely powerful research tool to develop medications that truly intervened in the genetic causes of brain diseases like schizophrenia, epilepsy and depression. MousePhenomics was also the proof that the cross-pollination between science and business that FES intended worked well and achieved good results – in terms of scientific progression and valorisation as well as economic spin-off. It was all the better for both patients and the economy: we are now on the verge of finding medicines against at least five brain diseases and, as for the economy, we have set the standard in mouse models for brain research – with a flourishing commercial spin-off as a result. It is just such a pity that FES has had no sensible follow-up. It is so very much worth it, for both patients and researchers, to also investigate the effects of the medicines that we are developing on social behaviour through lab animal models. That would render an even better model simulation of brain diseases. With the termination of the FES scheme, on the one hand, and the continual honing of the supervision on the use of lab animals, on the other hand, the chances of NeuroBasic SocioPhenomics are very slim.

Chris de Zeeuw
PROGRAMME DIRECTOR AND PROFESSOR OF NEUROSCIENCES AT THE ERASMUS UNIVERSITY MEDICAL CENTRE ROTTERDAM

Content

Introduction     3
Developing medicines for brain diseases     4
NeuroBasic in a nutshell     6
The treatment of schizophrenia begins with understanding     8
Mice with epilepsy     13
Ingenious equipment makes brain research easier     16
‘It is not an automatism; you will be disappointed sometimes’     22
NeuroBasic partners     24
Colofon     25
Developing medicines for brain diseases

Brain diseases score far below cancer and cardiovascular diseases in the mortality statistics. Their impact is, therefore, often underestimated. The effect of illnesses, such as depression, epilepsy, autism, and schizophrenia, on the quality of life and the costs involved in their treatment and the sick leave that they cause are, in fact, enormous.

Apart from their underestimated impact, these diseases have something else in common: there is no medication for them. However, if it is up to the NeuroBasic consortium, that is about to change. The consortium developed a method whereby chemicals can be specifically developed for the suppression of epileptic fits or combatting schizophrenia.

The main problem with brain diseases was that medicines could not be tested in any way. A great number of ethically irresponsible experiments have been conducted throughout history, where people were used as guinea pigs. Pharmacology uses animal lab tests as a rule, but as no one could say whether a mouse suffered from schizophrenia or not, let alone if it could be induced in them, developing a medicine for a brain disease was a perilous undertaking.

"In NeuroBasic’s predecessor, we developed a method to make mice suffer from the very specific genetic defect that leads to a brain disease in humans", Chris de Zeeuw, Programme Director and Professor of Neurosciences explains. "For each of the brain diseases, we then very carefully recorded the mice’s aberrant behaviour. Such observation and recording is vital. For diseases such as cancer or cardiovascular disorders, it is often at the cellular level that you can see the effects of your medicine and whatever is going right or wrong. For brain diseases, you will have to deduce it from the lab animal’s behaviour."

Considerable innovations were required before the mice’s behaviour could actually be recorded: a method to switch genes on and off as necessary, tests which measure accurately the extend to which a subject is suffering from the condition which should be caused by the genetic mutation, and a registration system that could record and analyse the behaviour of hundreds of mice at the same time.

"The Netherlands is the only country where so many scientists involved in so many different disciplines are so close together. We have people with a more than considerable understanding of, for instance, behaviour, brains, nerves, and the limbic system as well as the software and technology that we need to rapidly screen mice without causing them any stress. There is nowhere else in this world that you can get so many experts together, not in the academic world nor in the pharmaceutical industry."

It was a start. With sick mice now in hand, the great challenge for NeuroBasic was to develop effective ingredients for medicines. This was followed by tests on lab animals, so that it became clear whether the medicine-to-be was doing what it should. The next step was to gain some insight into why a medicine worked, or did not work, in mice. Some researchers had to go back to the drawing board.

The last step which was taken before the clinical tests began was possibly the most exciting. Being able to treat an epileptic mouse is one thing – whether it also works in humans still remained the question. “We people have similarities to mice. However, we had already seen that even if a compound affects the synthesis of one specific protein and this synthesis is the same in mice as in humans, there are still differences in what the body does with the medicine or the protein”, De Zeeuw clarifies. That is why the researchers will remain in suspense until the very last clinical trial. However, De Zeeuw believes that NeuroBasic’s chances of not only bringing lab animal tests to a new level, but also actually yielding medicines against autism, neurofibromatosis¹, tuberous sclerosis², epilepsy, and schizophrenia are considerable.

¹ Neurofibromatosis is the body’s hereditary inability to make neurofibrin – with a wide range of symptoms, varying from café au lait spots to learning problems.
² Tuberous sclerosis is usually a genetic mutation, with wide-ranging consequences such as epilepsy, autism, a mental handicap, skin disorders, and kidney diseases.
NeuroBasic in a nutshell

The development of medication for brain disorders has always fallen short of definitive success because their effectiveness will not be known until it comes to the fore in behaviour. That is why their development has been a matter of trial and error.

1. Sperm and ova are purposefully made to genetically mutate. This causes genetic defects.
2. The mice are screened to find out whether they have the correct defect.
3. Standardised tests help to ascertain each mouse’s specific brain disorder, such as epilepsy, schizophrenia or Parkinson’s.
4. A medicine is designed on the basis of the genetic defect.
5. The mouse is administered the medicine, after which its effect will be analysed.
6. If the medicine does not have the desired effect, it will be refined – or the researcher goes back to the drawing board.
7. The next step is to determine the reason why the medicine is working well.
8. An effective medicine for a mouse is not automatically effective in humans. The researcher now has to find out if the medicine would work the same in humans.
9. A clinical trial is to be conducted.
10. The medicine is ready.
The treatment of schizophrenia begins with understanding

Daily life is not easy for people who suffer from schizophrenia. Medication can help to suppress the symptoms, but the side effects are rather harsh. Steven Kushner, professor of Neurobiological Psychiatry at the Erasmus University Medical Center and NeuroBasic researcher is looking for alternative treatments, but: “the disorder is difficult to understand and it is a giant leap from lab animals to humans.”

Schizophrenia is sometimes commonly called a “split personality” with numerous alter egos. In reality, the disease has nothing to do with multiple personalities but rather with a broken thinking process. Schizophrenia affects the patient’s way of thinking. Their walking, talking, eating or sleeping remains the same, but it is fundamentally difficult for the patient to understand the world around them. Kushner: “We see things around us and can immediately distinguish whatever is important or can be ignored; we see what is real and what is not. This is far more difficult for someone with schizophrenia. If, for instance, I am on my own, daydreaming about a conversation, I, as a healthy person, know: this is not real, this is a daydream. A schizophrenia patient, on the other hand, can experience the daydream conversation as reality. That makes their life very complicated.”

On top of the unpleasant problems comes the nasty stigma of the disease, Kushner continues: “When a person is ‘talking to themselves’, alarm bells will soon go off in his environment: something’s not right here. We think it scary. We might feel uncomfortable when we see..."
someone injecting insulin, but we immediately know why and find it normal.”

Around one half to one per cent of all adults have schizophrenia. This percentage applies to every population group. The disorder reveals itself from the age of twenty and is chronic: schizophrenia cannot be cured. There is medication available and these make a considerable difference, according to Kushner. “In the times when we had no medicines, a patient had to stay virtually continuously in a psychiatric hospital. Fortunately, those days are over. Yet it is still difficult for patients to utilise all their potential and lead a happy, productive life. Medication is quite something.”

Antipsychotics – the type of medicine that most patients take – result in dulled emotions and a never-ending fatigue. Patients are no longer extremely sad, but nor are they extremely happy. Some people are better able to deal with these side-effects than others, but that does not mean that their lives can be compared with living without the schizophrenia. What is more, in the long term, the medication leads to abnormal movements, comparable with Parkinson’s disease, because the receptors in which the medicines interfere, are also important to movement.

The room for improvement, therefore, is mostly in diminishing the side effects. “You will hardly ever hear a patient complain: I wish that my medication had a better effect. It is always about the side effects, which can be so nasty that someone prefers not to take any medication at all”, Kushner says.

The NeuroBasic researchers went looking for ways to improve the medication, step by step. Firstly, you have to understand the disease. Like the majority of disorders, schizophrenia is caused by a combination of genes and, what researchers refer to as, “life experience”: food, lifestyle, accidents, environment, etc. However, which ratio of genes and life experience are determinant, is still to be established. “That is why we started the Genetic Examination into Neuropsychiatric Disorders or Gezin study (Gezin means ‘family’ in Dutch; ed.), a study among families where schizophrenia occurs”, Kushner continues. “The genetic component strongly prevails there, and so we could identify the genes that go with schizophrenia.” Knowing the specific genes would make it easier to study the disorder in lab animals.

In the quest for better medication, it was necessary to test the working of the different compounds. You can use lab animals for these tests but, fortunately, researchers have had other options for a few years. Brain cells like neurons can also be grown from induced pluripotent stem cells (IPSCs), adult skin or blood cells reprogrammed into stem cells. The way these active living brain cells behave is identical to the behaviour of brain cells from the body.

A little skin tissue from the participants in the study sufficed to grow IPSCs – firstly for the purpose of establishing the differences in the working of their brain cells, and secondly to test the effects of a compound. The researchers studied the morphology, gene expression and electrophysiological properties of the brain cells. “For schizophrenia it is important to look at the neuron level, as this is the level where, eventually, something goes wrong”, Kushner explains. “But we have also looked at the other brain cell types like oligodendrocytes (the cells responsible for the isolation of neurons so that they induce electrical impulses more efficiently; ed.), since the origin of the problem can be elsewhere.” Until now, the tests seem to indicate that it is primarily the oligodendrocytes (from IPSCs) that differ between schizophrenia patients and their healthy family members.

The researchers managed to identify a number of potentially effective compounds with the help of IPSCs. However, even if you know that a compound has the desired effect on a neuron, you still have a long way to go. The next stage was examining as to whether the compound had a good effect on the behaviour and performance of the individual as a whole.

“For this type of study, you cannot avoid working with lab animals.”

This is where the NeuroBasic working method came back into it. For the treatment of brain disorders, it does not suffice to merely look at the cellular level; it is actually the behaviour that...
is determinant: it is behaviour that shows whether the compound has the desired effect. Kushner: “For this type of study, you cannot avoid working with lab animals.”

Next, the compounds could be tested in the mice – to find out what they did to their behaviour, motor system, and cognitive functions. In order to assess a compound’s effect on the brain functions of a schizophrenic mouse, you can, for instance, entice a mouse to perform a task that requires memory and cognitive flexibility (see also: Ingenious equipment makes brain research easier). If a mouse has difficulty in changing a routine that it has been taught, it is an indication of a symptom of schizophrenia: inflexibility.

When it looks like the compound is working and the animal’s behaviour is improving, there is still no reason for a party. After all, the medicine also has to be effective in people. This step from lab animals to humans is gigantic. “A lab animal is not a person; it is the next best option: a model.” Before a compound that has to intervene in poorly functioning neurological circuits can be prescribed to a patient, it has to be absolutely clear that the physiological properties affected by the compound are the same for humans and mice. Even then, success is not guaranteed. Only a clinical study by the end of the programme can provide the true and definite answer.

There are multiple clinical studies into schizophrenia conducted at the moment, which all focus on improving antipsychotics and additions to the available range. The results are some time coming, but Kushner is positive: “NeuroBasic has booked so much progress when it comes to the treatment of psychiatric disorders – especially for the diseases that we knew more about when we started. We have now considerably increased our knowledge of schizophrenia. I have no doubt that this knowledge will eventually lead to far better medication.”

In a preceding NeuroBasic project, researchers successfully adapted mice in such a way that they can suffer from human diseases. Then, the first step is: check whether the mice do indeed show the associated symptoms. This is quite difficult for schizophrenia. Kushner: “We still do not know whether mice can really become schizophrenic. For people, the diagnosis is set by an interview and is based on someone’s thoughts and experiences – you can hardly do so with mice.” Still, the researchers managed to increase the risk of schizophrenia and induce its symptoms in mice through genetic and pharmacological manipulations, and are thus able to study the neurological mechanisms that are the cause of changes in the brains of patients with schizophrenia. “We have been quite successful in simulating in mice the neurophysiological changes in the brain as well as the cognitive and social disorders in people with schizophrenia”, Kushner says.

In the outer ends of the nerve cells, discrete the correct amount at the correct time – and that the next nerve cell absorbs them. This is how nerve cells “talk”. The defects in the protein disrupt this process. This is expressed in epileptic seizures and leads to mental retardation.

MUNC18 is not the only protein involved in the signal transfer of the brain. A number of proteins were already known to lead to brain disorders like schizophrenia, Alzheimer’s, ADHD, and epilepsy if defective. Neurobiologist Ruud Toonen, member of Verhage’s group, focused his search specifically on MUNC18. He is investigating how defects in this protein disrupt the signal transfer and how this relates to Ohtahara syndrome. “This protein is vital for the transfer of signals in the brain”, he emphasises. “No human or animal life is possible without this genome.”

Mice with epilepsy

Matthijs Verhage’s group within the NeuroBasic consortium is making mouse models for epilepsy by switching off a protein that is involved in the transfer of signals between nerve cells in the brain – neural communication. They are on a quest for medication specifically for brain disorders – with the help of a mouse with epilepsy.
MUNC18, the nerve cells cannot communicate. If it has a flaw, the balance in the signal transfer is upset.

**Smart medication**

This asks for medication that very accurately intervenes in this disruption of the nerve cells’ communication and repairs the “connection” – a remedy that can repair, or compensate for, the defect in the protein. Toonen: “But we first have to understand how exactly the mutation disrupts the communication in the brain – why the patient becomes ill. As soon as we know this, we can develop medication that is specifically aimed at changing or improving the protein. We want to develop medication that is ‘smarter’ than the existing medicines or works better.”

In order to develop such medication, you need a model in which you can study the defect as well as the defects that are at the bottom of Alzheimer’s, schizophrenia and other brain disorders. In the US, in the lab of Thomas Südhof – who was awarded the Nobel Prize in 2013 for his research into signal transfer in the brain, Matthijs Verhage created such a model for the Ohtahara syndrome. The result was a mouse model with a mutation in the MUNC18 protein: a mouse with epilepsy.

**Nonsense gene**

You can make this type of mouse model with stem cells that you extract from a very young embryo. These stem cells have usually not divided themselves as yet and can still grow into an entire animal. “Using DNA technology the MUNC18 gene is destroyed or replaced by a nonsense gene”, Toonen explains. With this technology you copy a small particle of a gene and put another particle in its place. When the cells divide, the nonsense gene is copied along. “We do so on one chromosome, one of the two parts of the gene – you have one of each of your parents. You will then end up with embryonic stem cells with one functional and one non-functional MUNC18. These mutated embryonic stem cells are replaced into the young embryo. They will then divide along with the rest while it grows into a mouse.”

**Black-and-white mosaic**

One part of the stem cells is, therefore, manipulated, but not all. In order to localise them at a later stage in the development of the mouse, the researchers take the stem cells that they manipulate from white mice and inject the mutated cells into a young embryo of a black mouse. Most of the pups that are subsequently born, have black fur, but some consist of both black and white cells: these grow into mosaic mice. “In these mice some of the egg and sperm cells will also be mutated and some won’t”, Toonen explains. “If you cross these mice and a pup is born from one of the mutated sperm cells, the pup will be completely white. It will get its father’s white coat. This pup has the mutation in all the cells on one chromosome, stemming from the father. The chromosome that stems from its mother is normal. The fur colour must be determined by the mutated embryonic stem cell in order to use it as a tell-tale.” This is the mouse model for Ohtahara syndrome.

**Translation**

They can change the research setting from a distance and let the mice perform tasks without disturbing them. “We have a test battery where we can observe a great many mice simultaneously. This way, we try to make the translation from the mutations in the genome to their behaviour”, Toonen explains. He shows a video of mice with a mutation in MUNC18, the lab animal model for the Ohtahara syndrome. On the left of the screen, a mouse is quietly walking around its cage and suddenly jumps straight up in the air. The mouse in the next cage is sleeping and seems to quiver all of a sudden – and again a few moments later. These are uncontrolled movements. The mice have seizures that resemble epilepsy. “Insofar as their behaviour goes, we see them jump and shake. But it is difficult to know for certain that it is epilepsy, for epilepsy is only defined with EEGs, brain films, in people.” A specialised laboratory in Germany will soon make EEGs in these mice. It will then become clear whether they have “real” epileptic seizures, or not.

**Medication**

The next step in the study is the search for compounds that can repair the disrupted signal transfer. Any molecule that compensates for the mutation in MUNC18 is a potential medicine. These kinds of compounds are designed by other research groups within NeuroBasic and the pharmaceutical industry. Toonen: “This all starts with a library of some hundred thousand molecules. This collection is reduced to about fifty candidates whose nerve cells we can test in a dish in order to find to what extent they affect the neural signal transfer. If these tests show that they improve it, you could, for instance, test the five most promising candidates in our mouse model. However, that is not until the very last stage – just before they are tested on humans, actually.”
The research by the NeuroBasic consortium has led to multiple spin-offs. Various companies are specialising in the development of hardware and software that contribute to better brain research – in lab animals and even in humans.

37 steps
A walking test to assess brain functions: that is the idea of the Erasmus ladder. The mouse catwalk was developed by Neurasmus, the neuroscientific company of Erasmus University. Because mouse genes can be adapted so as to simulate brain disorders, there is a need of tests that can measure the effects of both these disorders and the relevant medication, and this piece of equipment is just the thing for this: a horizontal ladder with 37 steps on each side, between two cages. Each step can change height on command. Mice are trained to walk from one cage to another with a constant speed, and the apparatus’ pressure sensors measure this speed as well as the mice’s stumbles and their jumps. “This way, you can not only thoroughly study a mouse’s walking behaviour, but also the way in which it learns a new walking pattern”, Chris de Zeeuw, Programme Director and Professor of Neurosciences at the Erasmus University Medical Center Rotterdam says. If the position of the steps changes so that an obstacle appears, the mouse has to shift its legs in order to avoid it.
Up to 350 times
This mouse has the option of three holes to climb through. If it picks the correct one, with the green arrow, it will get a treat. If it chooses the wrong one, nothing happens. It looks simple enough. However, the mouse will only get its nice snack every fifth time that it crawls through the correct gate. An ordinary mouse usually takes an hour or two to learn which hole it should choose. This makes it a suitable task to study Alzheimer’s, for instance, Maarten Loos of bioinformatics company Sylics, the developer of this CognitionWall, explains. “The cognitive performance of mice that develop brain damage like Alzheimer’s is poorer and they take significantly longer to execute this task. They will have to try for up to 350 times before they get the hang of it. So, if you give these mice a substance that should counter Alzheimer’s disease, you can hereby check whether it is effective enough to speed up learning and memorising.” The test is also a useful tool for schizophrenia: if you change the correct entrance after a while, the mouse should be flexible enough to notice.
Eons of time
This line-up of mouse cages looks common enough. Nevertheless, they are ingenious apparatuses: mouse after mouse can be watched without any need of a hands-on researcher. The lids house a camera that meticulously follows the animals’ every movement and sends it to a computer. The software analyses the video images and provides the researcher with an overview of the endless ramblings of their lab animals. Different colours indicate to where the mouse has stood still for a long time, which corner of its cage it likes best, or which route it prefers. In many lab animal studies it is useful to study such types of movements, for instance if you let them perform a task like the CognitionWall or an anxiety test. After all, you want to know how quickly a mouse learns. However, it normally takes eons of time. Hence the PhenoTyper, a cage with associated software developed by information technology company Noldus.
Dozens of mice can each go their own way in their own cage, and they are all automatically observed. “The fact that the PhenoTyper is fully automatic and can be configured for all kinds of tests makes it so popular among scientists”, Lucas Noldus, general director, explains. “It is also a commercial success: we have already sold over a thousand of these cages with instrumentation and video tracking software.”
‘It is not an automatism; you will be disappointed sometimes’

The principle behind NeuroBasic is to test medication in lab animals in a useful way, in cases wherein the disease that the medication needs to cure is mostly expressed in the animals’ behaviour. However, a mouse is still a thirty-gram lab animal with long whiskers. So, is a mouse really a suitable model when it comes to inducing human disorders? We give the floor to Chris de Zeeuw, NeuroBasic Programme Director and Steven Kushner, Schizophrenia Transworkpackage Leader.

Why did you opt for mice as lab animals?
De Zeeuw: “We share 97 per cent of our genes with mice. This means that a great many genetic defects that are behind our non- or misproduction of proteins cause identical problems in mice. Moreover, a mouse can easily be manipulated genetically, is simple to keep, procreates rapidly and without further ado, and is cheap – hence its suitability as our lab animal.”

Still, there have been cases where medicines worked well in mice, but the eventual clinical trials were disappointing.
De Zeeuw: “That happens. We have also seen that happening within NeuroBasic. In practice, it then turns out that even though a process has the same genetic origin in mice and humans, the degree to which the genes come to expression differs. That is why it is so important to stay on top of things as soon as you translate results to a human being: it is not automatically true that it works the same in humans. Sometimes you will be partially disappointed. But then it is still interesting to see what exactly is, and what is not, comparable.”

Kushner: “A lab animal is not a person: the mouse is explicitly a model, not the real subject. That makes it difficult. We have to carefully ascertain which parts of their physiology are comparable or in fact completely different.”

You could also use another lab animal.
Kushner: “Sometimes you might be better off with zebrafish or fruit flies, but for our type of brain research it is essential that the model brain is similar to ours. The brain must be as developed as possible, but at the same time the animal itself should suffer the least. Primates as potential lab animal models come too close: their emotions are very similar to ours.”

De Zeeuw: “There is no better model. Whatever animal you choose, the step from lab animals to humans remains crucial. It is especially because we are very similar to other mammals but we differ from them too that something which looked very promising can turn out to be not, or only partially, successful.”

The fact that lab animals sometimes prove not to be such a good model after all is used by lobbyists as an argument for abolishing lab animal testing altogether. What is your opinion on this issue?
De Zeeuw: “I have sympathy for the moral principle that each lab animal is one too many. I believe that you should only sacrifice lab animals if there is a realistic chance that they will help you acquire new knowledge. When I first started out as a researcher and had to kill my first rat, I actually considered a career change. But the reality is that we simply have no alternative. There are no lab animals in the kingdom of mammals more suitable for genetic manipulation than a mouse, and you can only do without any lab animals whatsoever in some cases by testing on cultivated tissue but the tissue still has to come from somewhere. If researchers can do without it, they will. But tissue does not show whether it is depressed or epileptic – only the behaviour of a living organism does.”

Kushner: “At the end of the day, no patient would like to test medication that could harm them. If you take lab animals completely out of the equation, you would take an enormous risk. Not everything can be tested on computer models or cultivated cells. However, it certainly is not a matter of scientists loving to work with lab animals. I am still hoping for the day that we don’t need them anymore. If there would be an alternative that was just as good – or even if it would just come close – I would be happy to adopt it, and a great many others too.”
NeuroBasic PharmaPhenomics is a Dutch public-private consortium that is working on the next generation of drugs for brain disorders. Central to their approach is the eventual large-scale and rapid design and testing of potentially effective compounds that can serve as a basis for medication against brain disorders. The increased understanding of complex signal transduction routes has led to the identification of a great number of candidate genes for major brain disorders as well as the development of specific mouse models. These new models are pivotal in making pre-clinical research into neurological and psychiatric conditions more efficient and ultimately in developing new treatments for human patients.

Contact: Arjen Brussaard, arjen.brussaard@vu.nl, +31 20-5987003