

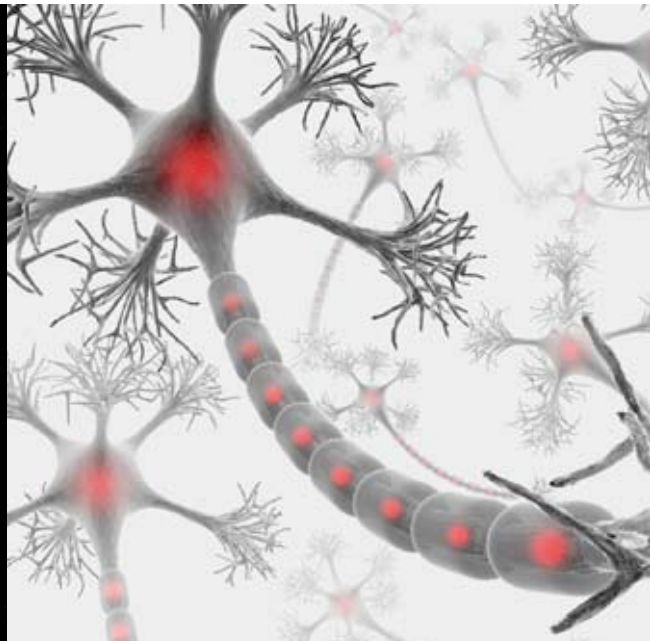


Joint workshop

# Brain diseases in the picture

*Molecular imaging and diagnostics for new therapeutic strategies in the central nervous system*

Jaarbeurs Utrecht, 16 June 2010



# Brain diseases in the picture

Molecular imaging and diagnostics for new therapeutic strategies in the central nervous system

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' Translating science into better healthcare '



' Jointly shaping the future of medicine '

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*Welcome to the workshop ‘Brain Diseases in the Picture’, organized by the Dutch public-private partnerships CTMM and TI Pharma.*

*Diseases of the Central Nervous System (CNS) constitute a major and growing burden. For example, in 2004 55.7 million patients suffered from Parkinson disease, Alzheimer’s disease or schizophrenia (three important and debilitating CNS diseases). Between 2008 and 2030 the share of these diseases in the global disease burden will increase by about 40%. For CNS diseases major diagnostic and therapeutic challenges remain. However, in recent years translational technology has evolved that could help pave the way for better diagnostic approaches and new, more effective medicines with fewer side effects.*

*TI Pharma and CTMM, both technological top institutes, focus on the translations of research findings to proof of concept for new products and services in healthcare. TI Pharma focuses on drugs, CTMM has its focus on diagnostics. The initiative of organizing this workshop lies in the overlapping part of these focus areas. Innovations can be realized thanks to the sharing of knowledge and close, multidisciplinary collaborations. New research findings are needed in the combat against brain diseases.*

*In this workshop experts from academia and industry will shed light on different aspects of major CNS diseases and demonstrate how advanced methods such as imaging, bioinformatics, mass spectrometry and microdialysis can help designing better diagnostic tools that will allow targeted clinical interventions at an earlier stage in selected groups of patients.*

*We wish you a very interesting and fruitful workshop.*

*Kind regards,*

*Daan Crommelin  
TI Pharma Scientific Director*

*Peter Lujten  
CTMM Scientific Director*

## Program

- 8:45 *Registration*
- 9:30 *Opening by **Daan Crommelin, TI Pharma***
- 9:40 **Markus von Kienlin, F. Hoffman-La Roche**  
*“MR biomarkers in Alzheimer and other neurodegenerative diseases”  
An industrial perspective*
- 10:15 **Karl Herholz, University of Manchester**  
*“PET for biomarkers in brain tumors and neurodegenerative diseases”  
An academic perspective*
- 10:50 *Coffee break*
- 11:10 **Marcel Verbeek, Radboud University Nijmegen Medical Centre**  
*“Biomarkers in CSF for neurodegenerative disorders,  
from academy to industrial application”*
- 11:45 **Eus van Someren, Netherlands Institute for Neurosciences**  
*“Imaging of pathology”*
- 12:20 *Lunch break*

## Program

- 13:00 **Ben Westerink, Groningen University**  
*“Microdialysis and microsensing: methods to monitor the role  
of neurotransmitters and biomarkers in the conscious brain”*
- 13:35 **Peter van der Spek, Erasmus Medical Center**  
*“Development of the Face and the Brain: Towards the Understanding of Molecular  
and Cellular Mechanisms, Linking Genotype to Phenotype”*
- 14:10 *Tea break*
- 14:30 **Peter Luijten, CTMM**  
*Overview, so far*
- 14:40 **Atul Butte, Stanford School of Medicine**  
*“Getting it all together”*
- 15:15 *Round table discussions*
- 16:15 *Closing & drinks*

**Markus von Kienlin**, Head of Magnetic Resonance Imaging and Spectroscopy, F. Hoffmann-La Roche AG, Basel, Switzerland



Since 1999, Prof. Markus von Kienlin is Head of Magnetic Resonance Imaging and Spectroscopy within F. Hoffmann-La Roche AG in Basel, Switzerland.

In this position, he has created a state-of-the-art MRI/MRS animal imaging laboratory, with the recent addition of a 9.4 T / 20 cm high-field instrument.

As a group leader within the Neuroscience department, he is responsible both for preclinical imaging studies to support drug discovery, as well as the design of human experimental medicine imaging studies for early drug development.

After completing his initial training at the Technical University in Munich, Germany, Markus moved to Grenoble, France, where he obtained his Ph.D. working on MRI/MRS in brain tumors. From 1989 to 1991, he was a postdoctoral fellow at the National Institutes of Health in Bethesda, USA, in the then newly created *in vivo* NMR Research Center. Returning to Germany, he spent eight years at the University of Würzburg where he obtained the German habilitation diploma, before finally joining Roche. Markus has (co-)authored over 80 publications on techniques and applications of MR imaging in peer-reviewed scientific journals.

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## Imaging Biomarkers in Drug Discovery and Development – MRI/MRS Examples from Alzheimer's Disease

There are great expectations on the various, rapidly evolving imaging modalities which allow a detailed look into both molecular processes and function in the human brain. These new technologies already have significantly advanced our understanding of many mechanisms in the brain, both at a molecular and at a system level; these “imaging biomarkers” thus should provide an earlier, better differentiated diagnosis of brain disorders, and ultimately a faster monitoring of the effect of therapeutic interventions.

Taking examples from Alzheimer's Disease (AD), the talk will show which MRI/MRS approaches are currently explored in human patients, in large trials such as the NIH-sponsored “Alzheimer's Disease Neuroimaging Initiative (ADNI).” Translating back to preclinical pharmaceutical research, it is shown how further imaging biomarkers are identified and characterized in animal models of AD. Using these examples, the value of imaging biomarkers for Drug Discovery and Development is elucidated, but also some pitfalls are highlighted.

*Karl Herholz, Wolfson Molecular Imaging Centre, University of Manchester, United Kingdom*



Karl Herholz graduated as a medical doctor at the University of Erlangen, Germany, in 1980. After basic general clinical training, he joined the Max-Planck-Institute for Neurological Research in Cologne, Germany, as a research fellow in 1982 and became professor of neurology at the University of Cologne in 1994. He moved to the University of Manchester, UK, in 2005 to become professor in clinical neuroscience and director of the Wolfson Molecular Imaging Centre ([www.manchester.ac.uk/wmic](http://www.manchester.ac.uk/wmic)).

His research focuses on neuroimaging studies (PET and MRI) in dementia and brain tumours. He has been coordinating collaborations on Early Diagnosis of Neurodegenerative Diseases within the EU-funded Network on Diagnostic Molecular Imaging ([www.dimi.eu](http://www.dimi.eu)) and was Chief investigator of the EU-funded “Network for Efficiency and Standardisation of Dementia Diagnosis” (NEST-DD) creating a comprehensive clinical and neuroimaging digital database of more than 1000 subjects.

## PET as a biomarker in brain tumours and dementia

Positron emission tomography (PET) utilises short-lived radioactive tracers, operating at micro- or nanomolar concentrations, to provide quantitative information on transport processes, metabolism, receptor expression, and drug effects in human tissue. Thus, they can provide tools for sensitive and early diagnosis and monitoring of disease progression and treatment effects, with main applications in Alzheimer’s disease (AD) and brain tumours (gliomas). <sup>18</sup>F-labeled compounds can be produced at central specialised centres equipped with cyclotron and radiochemistry for delivery to multiple hospitals for widespread application in clinical diagnosis and clinical trials.

The most widely used PET tracer is <sup>18</sup>F-2-fluoro-2-deoxyglucose (FDG), which is available from commercial distributors, for assessing glucose consumption. In brain tumour studies, it has been shown to differentiate high-grade gliomas from low-grades, provide prognostic information even within histological grades, and locate the most malignant part in gliomas for biopsy. However, due to high glucose consumption in normal cerebral cortex, it does not provide a good target-to-background contrast. Labelled amino acids, such as <sup>11</sup>C-methionine and <sup>18</sup>F-fluorotyrosine, provide better contrast to normal brain than FDG, show increased uptake even in low-grade gliomas in the absence of contrast enhancement on MRI, and provide information on the extent of infiltration in malignant gliomas. They are being used increasingly for planning and monitoring of brain tumour therapy. Labelled nucleoside analogues, such as <sup>18</sup>F-fluorothymidine (FLT), are being used to assess tumour proliferation. Amino acids and FLT have shown potential to assess early response to therapy in clinical trials.

In studies of AD and the prodromal stage of mild clinical impairment (MCI), FDG has been shown to identify MCI patients who are at high risk for progression to dementia within the next 2 years. Automated procedures are available to assess the severity of functional brain deficits, reflecting the severity of disease and thus having potential for use as biomarker in clinical trials. More recently, much interest has focussed on amyloid imaging with PET which provides a very sensitive tool to detect fibrillary amyloid deposits in human brain probably up to 10 years before onset of dementia. Because amyloid deposits also are the histopathological hallmark of AD, amyloid imaging is expected to provide a sensitive and specific biomarker for early diagnosis of AD and for monitoring of anti-amyloid treatment. Currently, several <sup>18</sup>F-labeled amyloid ligands are undergoing clinical trials to establish their utility.

*Marcel Verbeek, associate professor in Neurochemistry, Departments of Neurology and Laboratory Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*



Marcel Verbeek graduated in 1988 Chemical Technology at the Technical University Delft. After that, he worked as a researcher at TNO Leiden (Gaubius Institute), and moved on to Nijmegen to start a PhD project. In 1996 he received *cum laude* his PhD degree on research on the vascular and inflammatory involvement in Alzheimer's Disease (Faculty of Medicine, Department of Pathology, Radboud University Nijmegen Medical Centre). Since 1999 he is appointed as a neurochemist at the Department of Neurology (and since 2009 also at the Department of Laboratory Medicine) of the RUNMC. In this position he is heading the Dutch Reference Laboratory for CSF Diagnostics. This laboratory performs a lot of specialist diagnostics for many Dutch (and international) institutes.

His research is focused on the neurochemistry of neurodegenerative disorders, specifically dementia syndromes (such as Alzheimer's disease) and movement disorders (such as Parkinson's disease). One of the major aims of the research is to develop and validate biomarkers in body fluids (especially cerebrospinal fluid) for (early) detection and diagnosis of these disorders. To achieve this aim active collaborations are established with researchers / clinicians within the Alzheimer Centre Nijmegen and the Parkinson centre Nijmegen as well as with many international researchers. Besides this biomarker research, he is also interested in the study of the pathophysiology of Alzheimer's disease and Parkinson's disease. These type of studies focus on the aggregation properties of the amyloid  $\beta$  protein and  $\alpha$ -synuclein and their interactions with other proteins and cells in the brain.

### **Current function and organization**

Dr. ir. Marcel M. Verbeek is associate professor in Neurochemistry at the Radboud University Nijmegen Medical Centre, Departments of Neurology and Laboratory Medicine. He is heading the National Reference Laboratory for CSF investigations (diagnostics and research). The research is embedded in the Donders Centre for Brain, Cognition and Behaviour, a campus-wide research institute of the Radboud University Nijmegen, and in Alzheimer Centre Nijmegen (CAN) and the Parkinson centre Nijmegen (ParC).

There is an urgent need for biomarkers for (early) detection and prognosis of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Since the cerebrospinal fluid (CSF) is in close contact to the brain, pathological changes in the brain are thought to be reflected in the CSF. As such, the CSF may be a rich source of disease-specific biomarkers for neurodegenerative disorders. These searches have been successful to a variable degree.

In AD, CSF biomarker development has focused on amyloid  $\beta$  and tau proteins, which are the major protein as that accumulate in AD brains; in PD studies focused on the proteins such as  $\alpha$ -synuclein and DJ-1 that are linked to PD pathogenesis. Especially in AD, biomarker analysis have been incorporated into newly developed research criteria for the diagnosis of AD and currently many clinical trials rely on endpoints defined by biomarker measurements in addition to parameters of clinical outcome.

*Eus JW Van Someren, Head Dept. Sleep & Cognition, Netherlands Institute for Neuroscience,  
VU University Amsterdam and Leiden University Medical Center, The Netherlands*



Prof. Dr. Eus J.W. Van Someren was trained in physics, psychophysiology and neuropsychology and received a *cum laude* PhD in neurobiology from the faculty of medicine. He is Head of the Department Sleep and Cognition at the Netherlands Institute for Neuroscience, has a professorship at the VU University, Amsterdam, and a pending professorship at the Leiden University Medical Center. He received prestigious grants including the NWO-VIDI and VICI.

His ~100 peer-reviewed publications in scientific journals including *NJEM*, *Jama*, *Nature Neuroscience* and *PNAS* have been cited 2000 times (H-factor 25). His expertise covers sleep, circadian rhythms, cognition, aging, thermoregulation, imaging and acquisition and analysis of physiological and behavioral time-series. He recently founded the Netherlands Sleep Registry, a large-scale effort to facilitate progress in the understanding of risk factors, genetic predispositions and brain mechanisms involved in sleep and its disturbances. His informal and easy manner and infectious enthusiasm for sleep and cognitive neuroscience make him a frequently invited speaker for lay, neuroscience and medical audiences.

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## Brain Imaging reveals affected brain circuits in chronic insomnia, the most prevalent yet forgotten CNS disease at high age

Chronic insomnia is the most prevalent psychological complaint, affecting ~10% of the general population and up to 40% of elderly people. It has a strong impact on quality of life, productivity and sick leave, and is a primary risk factor for the development of depression, and likely cardiovascular disease and the metabolic syndrome as well. In spite of the huge cost for society, the underlying causes and rational treatment avenues have hardly been investigated with the rich set of advanced tools that modern neuroscience has available presently to tackle brain disease.

We showed in a voxel-based morphometric (VBM) MRI study that chronic insomniacs have a decrease in orbitofrontal gray matter volume that strongly correlates with the severity of sleep complaints, and may be involved in abnormalities in comfort sensing (*Biol Psychiatry* 2010 67:182-185). Using fMRI we demonstrated attenuated prefrontal activation (*Sleep* 2008 31:1271-1276), which reversed upon successful sleep therapy. On the other hand, using transcranial magnetic stimulation, we found an abnormal intracortical facilitation that did not recover after treatment. Thus some deviations seem reversible, while others may represent endophenotypes enhancing the risk of developing chronic insomnia.

To improve phenotyping we initiated the Netherlands Sleep Registry. This internet survey and task-assessment platform for extensive characterization of subtypes of good and poor sleepers that will facilitate selection of homogeneous subgroups for imaging studies – with the ultimate goal of obtaining the endophenotypes and genotypes that are necessary for a better understanding of the brain mechanisms of chronic insomnia and sound sleep.

**Ben H.C. Westerink**, head of research group *Biomonitoring and Sensing* of the department of Pharmacy, University of Groningen, The Netherlands.



Prof. Ben H.C. Westerink is head of the research group Biomonitoring and Sensing of the department of Pharmacy, University of Groningen. His area of research is *in vivo* monitoring of endogenous compounds (neurotransmitters, metabolites, modulators) in experimental animals and humans. He has published more than 200 papers in peer-reviewed journals and is one of the founders of the microdialysis technique. His special interest is the mechanism of action of centrally acting drugs. He is involved in the development of anti-parkinson (e.g. Neupro) and antidepressant drugs.

### **Current function**

Since 2004, prof Westerink is the scientific director of the Groningen Research Institute of Pharmacy (GRIP). He will retire in September 2010. Since 2002 he is the scientific director of the university spin-off company Brains On-line ([www.brainsonline.org](http://www.brainsonline.org)). The mission of Brains On-line BV is to provide preclinical research services (microdialysis, microsensing, electrophysiology, bioanalysis, behaviour etc) to facilitate the development of new drugs that target the central nervous system. The company provides services all over the world from research facilities in Groningen, San Fransico and Kurume.

### **Organizations:**

Groningen Research Institute of Pharmacy, RUG and Brains-on-line BV, Groningen, the Netherlands

## Microdialysis and microsensing: methods to monitor the role of neurotransmitters and biomarkers in the conscious brain

co-author: Thomas I.F.H. Cremers

### **Abstract of the presentation**

For a full pharmacokinetic and pharmacodynamic evaluation of an experimental drug that act on the central nervous system, levels in blood as well as in the extracellular space of the brain are required. In addition information about the effects of the compounds on the biochemistry of the brain (e.g. release of neurotransmitters or modulators) is needed. To that end we combine chronic implantations of blood catheters and microdialysis probes or sensors in freely moving laboratory animals (rats, mice, guinea pigs).

An established method to sample extracellular space is microdialysis. However the method lacks quantitative information as the recovery of the compounds through the dialysis membrane is low and unpredictable. Methods to circumvent this disadvantage require high amounts of experimental animals. We have recently developed a probe that samples exogeneous and endogeneous compounds with a recovery close to 100%. To optimize the bioanalysis of microdialysis and blood sampling we have developed sensitive derivatization methods that enables simultaneous determination by LC-MS-MS of a large series of amino acid and amine-derived neurotransmitters and related metabolites.

A method that has a higher spatial (10-25  $\mu\text{m}$ ) and temporal (second-scale) resolution than microdialysis is microsensing. Microsensors are directly implanted in subcutaneous and brain tissue and are able to capture fast changes in neurotransmitter levels, glucose or other physiological compounds. Wireless connections with the animals provide unrestraint recordings.

**Peter van der Spek**, Professor and Head of department of Bioinformatics at Erasmus MC, Rotterdam, The Netherlands



Peter J. van der Spek has been appointed as professor and head of the department of bioinformatics at the Erasmus MC. He obtained his doctoral degree in 1995 in the field of molecular carcinogenesis by cloning cancer predisposition genes.

Van der Spek has 6 years of pharmaceutical experience from Akzo-Nobel and Johnson & Johnson and holds several international academic appointments in Japan, Australia and USA. The bioinformatics group at the Erasmus MC focuses on the support of data mining and analysis. This expertise is used for fundamental research, molecular diagnostics, molecular imaging, (forensic) molecular biology and support of clinical trials. Erasmus MC is one of the largest medical centers of the Netherlands. Van der Spek runs a neuroscience research program which provides the biological and technological basis for the bioinformatics group. It concentrates on the way the genome as a whole contributes to the evolution, development, structure and function of the brain.

#### **Organization:**

The largest center of its kind in the Netherlands, Erasmus MC provides advanced medical care to 3 million people living in the southwestern part of the Netherlands. Care is organized in three clinical branches: the General Hospital; the Sophia Children's Hospital and the Daniel den Hoed Oncology Center.

Erasmus MC has achieved excellence in many areas, including cardiovascular diseases, oncology, pediatrics, genetics and cell biology, human reproduction, endocrinology, microbiology and virology, immunology, hepatology and (micro-) surgery.

Erasmus MC is among the top research institutes in the Netherlands and participates in several nationally and internationally recognized research schools. Research activities range from fundamental biomedical research, patient-related research and epidemiology to public health, health care policy and management.

#### **Fundamental Research**

The Erasmus MC department of bioinformatics runs a research program of its own, which provides the biological and technological basis of all its activities. The program concentrates on the way the genome as a whole contributes to the evolution, development, structure and function of the brain.

This involves analysis of (next-generation) sequencing data, promoter/enhancer data, copynumber variation and gene expression in more than 50 different human brain regions.

Our approach aims on integrating genomics, proteomics and cytogenetic data with medical imaging data to identify genes associated with neuro-development, neuro-degeneration and neuro-oncology.

#### **General Description**

The aim of our research is to gain insight in the molecular and cellular mechanisms driving the development of the face and the brain. The molecular signals that mediate these brain patterning events are, for the most part, unknown. During development and in mature organisms, cells respond to changes in their environment in part through changes in gene expression. Extracellular factors including growth factors, hormones and neurotransmitters activate programs of new gene expression in a manner that is temporally and spatially controlled by the coordinated action of trans-acting transcription factors that bind to cis-acting DNA regulatory elements including enhancers, insulators and promoters.

#### **Translational Research**

Multiple congenital brain and craniofacial disorders, including craniosynostosis, mental retardation, microcephaly, facial dysplasia and growth retardation derive from disruptions in early progenitor mesenchymal stem cells. Medical 3D-imaging data is obtained from prenatal diagnostic examinations, neonatal examination, and children suffering from congenital malformations as well as post mortem biopsies from normal and diseased brain tissue specimens for genetic analysis. Elucidating these cellular and molecular mechanisms that regulate the patterning and differentiation of forebrain, midbrain and hindbrain in 3D together with tractography data provides novel insight in the complex circuits of the human brain. Molecular imaging techniques using brainbow mice provide understanding of the connectome using 3D virtual reality. Our research provides novel insights crucial for genetic diagnostics/counseling, molecular pathology and image guided intervention.

**Atul Butte**, Assistant Professor of Pediatrics and Medicine (Informatics) and, by courtesy, Computer Science, Stanford University and the Lucile Packard Children's Hospital, and pediatric endocrinologist, USA



Atul Butte, M.D., Ph.D. is an Assistant Professor in Pediatrics, Medicine (Medical Informatics), and by courtesy, Computer Science, at Stanford University and the Lucile Packard Children's Hospital, and is a pediatric endocrinologist. Dr. Butte's laboratory focuses on solving problems relevant to genomic medicine by developing new methodologies in translational bioinformatics. Example of his lab's work includes work on cancer drug discovery (Proceedings of the National Academy of Science, PNAS, 2000), type 2 diabetes mellitus (PNAS, 2003), fat cell formation (Nature Cell Biology, 2005), and transplantation (PNAS, 2009).

To facilitate this, the Butte Lab has developed tools to automatically index and find genomic data sets based on the phenotypic and contextual details of each experiment (Nature Biotechnology, 2006), re-mapping microarray data (Nature Methods, 2007), and deconvoluting multi-cellular samples (Nature Methods, 2010). The Butte Lab has also been developing novel methods in conducting basic science using electronic health record systems (Science, 2008), performed the first clinical evaluation of a whole human genome (Lancet, 2010), and reported the first Environment-Wide Association Study (EWAS; PLoS One, 2010). Dr. Butte has authored more than 80 publications in bioinformatics, medical informatics, and molecular diabetes, and has delivered more than 110 invited presentations world-wide on bioinformatics.

Dr. Butte builds and applies tools that convert the billions of points of molecular, clinical, and epidemiological data measured by researchers and clinicians over the past decade into insights into diagnostic and therapeutic potential. Dr. Butte will highlight how using publicly-available molecular data enables the discovery of new gene variants and biomarkers for diseases like diabetes, suggests novel roles for drugs in the treatment of disease, and for the first time allows us to probe the inner commonality across disease. Dr. Butte will also discuss his recent papers on the clinical evaluation of a personal genome and the environment-wide association study (EWAS).

## About Top Institute Pharma

Top Institute Pharma (TI Pharma) is a public-private partnership in which scientific and business worlds work together on groundbreaking, multidisciplinary research aimed at improving the development of socially valuable medicines. Our research portfolio is based on the disease areas as specified in Priority Medicines, a report by the World Health Organization (WHO). These projects create knowledge that is important for better, faster and less-expensive development of valuable new medicines. For more information, please visit [www.tipharma.com](http://www.tipharma.com).

Key figures TI Pharma: 74 partners, M€ 260 allocated budget, 50 projects/consortia



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## About CTMM

The Center for Translational Molecular Medicine (CTMM) is dedicated to the development of molecular diagnostics and imaging technologies that enable the design of new and “personalized” treatments for the main causes of mortality and diminished quality of life (cancer and cardiovascular diseases and, to a lesser extent, neurodegenerative and infectious-/autoimmune diseases) and the rapid translation of these treatments to the patient. CTMM is a public-private partnership that comprises a multidisciplinary group of parties – universities, academic medical centers, medical technology enterprises and chemical and pharmaceutical companies. For more information, please visit [www.ctmm.nl](http://www.ctmm.nl).

Key figures CTMM: 107 partners, M€ 275 allocated budget, 21 projects/consortia



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