Translating science into better healthcare
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## CTMM history

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### ISAC TRACK

- **February**: First Call Proposal Assessment
- **February**: Second Call Proposal Assessment
- **January**: Joint Call Proposal Assessment ISAC Site visits
- **May**: First Call Projects Mid-term Review
- **January**: Joint Call Projects and TraIT Mid-term Review

### START-UP TRACK

- **June**: Start of 10 Projects
- **May**: First Call Projects Mid-term Review
- **January**: Final Call Projects Mid-term Review

### PRODUCT TRACK

- **February**: Final Assessment stage 1
- **November**: Final Assessment stage 2 and Recommendations

### CTMM TRACK

- **September**: 1st call for Proposals
- **February**: First Call Proposal Assessment
- **February**: Second Call Proposal Assessment
- **January**: Final Call Projects Mid-term Review
- **January**: Joint Call Projects and TraIT Mid-term Review
- **January**: Final Call Projects Mid-term Review
- **February**: Final Assessment stage 1
- **November**: Final Assessment stage 2 and Recommendations

### ISAC site visits

- **May**: First Call Projects
- **January**: Joint Call Projects and TraIT Mid-term Review
- **September**: Valorization Call
- **September**: Joint Call with IMM / TI Pharma
- **June**: Start of next 10 Projects
- **June**: Start of first 8 Projects
- **June**: Start of 3 Joint Call Projects

### Valorization Projects

- **September**: Valorization Call
- **September**: Valorization Call
- **September**: Valorization Call

### Research Pearls and TraIT Transition Grants

- **December**: Research Pearl and TraIT Transition Grants
- **December**: End of FES 2006 Funded Projects
- **December**: Research Pearl and TraIT Transition Grants

### Projects

- **QVQ**: Glycoscheck, Mirabilis, Miraest
- **Glycocheck**: Miraest
- **Glycoscan**: Miraest
- **SelectMdx**: Miraest
- **PreselectSCAN Assay**: Miraest
- **MM Profiler**: Miraest
- **TAE Profiler**: Miraest
- **TCF / Aveo Pharma**: Miraest

### Infrastructure

- **Philips HF Point-of-care device**: TAE Profiler
- **Trombin Generation Assay**: TAE Profiler
- **Volta HIFU system**: TAE Profiler
- **TraIT infrastructure**: TAE Profiler

### Other Projects

- **Glycocalix Measurement System**: SelectMdx
- **NIRF Camera**: SelectMdx
- **TCF / Aveo Pharma**: SelectMdx
- **MyRhythm**: SelectMdx
- **Age Reader**: SelectMdx
- **AML Profiler**: SelectMdx
- **Philips HF Point-of-care device**: SelectMdx
- **TriPeak Generation Assay**: SelectMdx
- **Volta HIFU system**: SelectMdx
- **TraIT infrastructure**: SelectMdx
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Created in 2007, and funded by the FES (Fonds Economische Structuurversterking), the Center for Translational Molecular Medicine (CTMM) represents the largest and most comprehensive Technological Top Institute (TTI) in the Dutch life sciences. The explicit aim of its business plan was to enable clinicians to take major steps forward in addressing the main obstacles to effective healthcare: the (too) late diagnosis of disease, medication that is ineffective or has serious side effects, and delays in translating therapeutic innovations out of the lab and into clinical practice.

The CTMM ambition was to significantly reduce the impact of some of the world’s most prevalent lethal and debilitating diseases, such as cancer, cardiovascular disease, and neurodegenerative diseases such as Alzheimer’s. People who have to live with disease should enjoy the best quality of life possible. The CTMM ambition was to significantly reduce the impact of some of the world’s most prevalent lethal and debilitating diseases, such as cancer, cardiovascular disease, and neurodegenerative diseases such as Alzheimer’s. People who have to live with disease should enjoy the best quality of life possible. Molecular medicine provided the scientific base for the CTMM ambition. It is the bridge between fundamental scientific knowledge and new clinical solutions that improve the quality of healthcare and create sustainable economic growth, and generate employment. This ‘golden triangle’ of government support and public and private partners was reinforced by the participation and support of major medical charities – the Dutch Arthritis Foundation, Dutch Cancer Society, Dutch Diabetes Research Foundation, Dutch Cystic Fibrosis Foundation, Dutch Heart Foundation, and Dutch Kidney Foundation. In Chapter 2 of this book, many of the stakeholders in this large enterprise reflect on the lessons learned and the benefits accrued from the program.

The impact of the CTMM ambition was high, and although some of these ambitions have not yet been fully realized, the impact of the CTMM program on the Dutch life-sciences landscape has been substantial. The program has so far yielded more than 140 test devices (both point-of-care and lab-on-chip) that have been produced, some of which have already been CE-marked and introduced into the market. Numerous software applications have been written and disseminated, ranging from data analysis programs to risk calculators for specific diseases. An image-guided treatment platform to treat breast cancer using focused ultrasound has been developed and tested in phase 1 & 2 trials, and a new camera for visualizing tumor tissue during surgery has been introduced into the surgical suite. Numerous software applications have been written and disseminated, ranging from data analysis programs to risk calculators for specific diseases. An image-guided treatment platform to treat breast cancer using focused ultrasound has been developed and tested in phase 1 & 2 trials, and a new camera for visualizing tumor tissue during surgery has been introduced into the surgical suite. All of these solutions and products will have a major impact on screening and prevention, patient stratification, and treatment delivery and monitoring. The impressive portfolio of achievements by the CTMM consortium covers a large collection of use cases in personalized medicine. Despite the fact that the funding of large-scale innovation programs in the Netherlands has largely been discontinued, many CTMM consortium partners have continued to work closely together to translate breakthroughs in medical biology into new clinical solutions.

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Chapter 2 Patient benefit

Meeting real patient needs

In January 2011, the Health Council of the Netherlands (Gezondheidsraad), an independent scientific advisory committee for the Dutch government, published a report titled ‘Medical products: new and needed! - An investment strategy for research into innovative and relevant medical products’. In defining relevant research, the committee focused on the wishes of those who make use of medical products – patients and their care providers.

The outcome of the report was a methodology for setting research agendas from the perspective of users, and the beginning of a medical products research process.

In the past, many charitable foundations had already followed the wishes of those who make use of medical products – patients and their care providers.

For many of the Netherlands’ charitable foundations, however, it came as no great revelation to CTMM. It was already well on the way to putting patients squarely at the center of its translational research.

During its strenuous efforts to acquire additional funding for its projects, CTMM had heard that message loud and clear from the charitable organizations it would later become its supporting foundations. By 2011, CTMM was already on the way to putting patients squarely at the center of its translational research.

CTMM’s recommendation was that regular dialogue meetings should be held between users, researchers and developers with the aim of gaining early insights into long-term product development.

In order to extend this patient centered approach to the involvement of patients in setting research agendas, CTMM collaborated with the Center for the Society and the LifeSciences (CS2) to set up and fund a project aimed at identifying ways in which patient involvement could be achieved. One of the results of that came out of this project was a decision support tool that helps research groups to decide when and how to involve patients. In addition, CTMM cofunded the development of a card-based tool for patient participation in decision making related to diagnosis.

The hope is that such initiatives will add to the patient involvement and therefore embraced CTMM’s activities on this issue. Patients are now more represented on the foundations’ scientific advisory committees for larger projects.

Most of CTMM’s supporting charitable foundations were already following the trend towards increased patient involvement and therefore embraced CTMM’s activities on this issue. Patients are now more represented on the foundations’ scientific advisory committees for larger projects.

Has the CTMM-public-private partnership accelerated ‘bench to bedside’ translational research?

The supporting foundations acknowledged that academic researchers typically don’t know how to bring new knowledge to the market, whereas commercial companies do, and that bringing those two worlds together is a key to accelerating ‘bench to bedside’ translational research.

As a result of their participation they also reported that they now have a much wider network of contacts, allowing them to act as brokers in bringing people together in new public-private partnership initiatives and ecosystems. CTMM was regarded as a practical example of how to generate these ecosystems.

What measures for patient participation came out of your CTMM involvement?

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Patient focused - start to finish

Maarten van der Weijden, who recovered from leukemia as a result of stem-cell therapy and went on to become the 2008 Olympic Gold Medallist for the men’s 10-km open-water swimming event, speaking at one of CTMM’s Networking Days - living proof of what translational medicine is all about.

In June 2012, a group of eight cyclists from CTMM entered the grueling Alpe d’Huzes cycling event with the aim of raising 30 thousand Euros for cancer research. For CTMM, the Alpe d’Huzes slogan of ‘never give up’ was particularly close to its heart, because its own philosophy throughout the program was never to give up on translating scientific research into better healthcare.

How did the CTMM program influence your funding allocation and project supervision/management processes?

All the supporting foundations stated that participating in CTMM had made them more aware of how to give substance to their corporate social responsibility in terms of ensuring that the projects they fund actually end up benefiting patients and the healthcare system. As a result, they now demand to know more about what their money will be spent on in terms of the quality, relevance and feasibility of the research, making it easier for them to have submitted proposals evaluated by patients and in the (near) future also by venture capitalists.

“CTMM experience has been a turning point to focus on corporate social responsibility and how to ensure patient benefit faster.” Anneke Mels, Dutch Digestive Foundation

In terms of project supervision and management, several supporting foundations are applying the CTMM model in new initiatives, leveraging its focus on project monitoring and supervision to prove to donors that they are investing their donors’ money wisely. CTMM was a testing ground that allowed the charity foundations to make the transition from mere financial partners to active project partners.

Which elements of the FES funded CTMM research programs should be conserved for the future?

Keeping the networks alive and conserving knowledge of how to run public-private collaboration in terms of methodologies, processes and contracts, were considered the two most important elements to conserve for the future.

“It is a pity that CTMM will not be continued in spite of all successes.” Ingrid Leheu, Dutch Arthritis Foundation

RECOMMENDATIONS

The charitable foundations concluded with the following recommendations for the future:

• The trend towards increased patient involvement in setting research agendas should be continued
• Consortia should be limited to a maximum of 10 partners or partner involvement restricted to specific research tasks or phases to facilitate effective project management
• Partnerships should extend beyond national borders to leverage world-class expertise from Europe and beyond
• Medical Health Technology Assessment (MHTA) should be an integral part of new project proposals
• Governance should be based around proven models such as CTMM
• New funding schemes should be explored that do not involve government money so that research programs are not affected by changes in government policy

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Innovation and the Continuum of Care

The process of medical research and innovation comprises several phases, all of which have to be taken into account if the end results are to have a real impact on healthcare. Research, development, validation and implementation represent the end-to-end translational journey for every new medical solution before it reaches the patient, irrespective of whether the solution relates to diagnosis or treatment (care and cure). However, despite the fact that virtually all new developments require extensive research and large investments, it is not always the most complicated technology or the most expensive medication we will need to combat disease.

In the same way that translational research involves a number of phases, modern healthcare systems deliver the cycle of care in a number of steps, all of which are indispensable for sustainability and accessibility. The first steps are disease prevention and prognosis. Can we design models that identify each individual person’s risk of contracting specific diseases? Which prevention strategy optimally mitigates these risks?

The next steps are diagnosis and treatment. Will early detection of disease enable better prognosis? If several treatment options exist, which one will serve an individual patient best? Can we design targeted therapies that are highly effective yet minimize side effects? Can we monitor the therapeutic effects of treatment early enough to prevent overtreatment and patient discomfort? Can we develop monitoring devices that will help us to decide whether patients are actually under the optimal treatment regime?

Just as importantly, can we lower the cost of the developed solutions to the level needed to ensure the sustainability, affordability and accessibility of healthcare?

Focusing on the continuum of care, CTMM has created a collaborative community of academic and industrial scientists, medical technology assessment experts and entrepreneurs. Together, they have made important steps to providing the answers to these questions, many of which address the most important challenges in healthcare.

These challenges include developing better diagnostics and therapies for the most prevalent forms of cancer, for obesity-related cardiovascular disease, for chronic heart failure, and neuro-degenerative and infectious diseases such as Alzheimer, rheumatoid arthritis and sepsis.

Within the CTMM community, large public-private partnership (co)alitions worked closely together, not only on pre-competitive research, but also on product development and clinical implementation. What follows are noteworthy examples of what has been achieved within CTMM to cover the complete continuum of care. Researchers in the life sciences often refer to the ‘4P’ principle: Predictive, Personalized, Preventive and Participatory medicine. These four Ps are as relevant to the entire CTMM program as they are to the life sciences in general. Improved diagnosis based on personalized assessment for disease prevention, prognosis, treatment prediction and treatment guidance has been one of the key drivers for the CTMM program. In collaboration with health organizations that have close ties to patients and patient advocacy groups, CTMM has made substantial steps forward in all of these domains.
Prevention

The earlier, the better ... the metabolic imprint of our cardiovascular system

Prevention is always better than cure. For some diseases, particularly those of the cardiovascular system, healthy living may have substantial protective and preventative benefits as well as contributing to longevity and improved quality of life. In terms of prevention, our individual molecular programming is partly predetermined by dietary conditions during the pre- and early postnatal period – a process known as metabolic imprinting. These conditions are the set points for our energy balance, determining our glucose and lipid homeostasis. Dysregulation of these set points is known to be associated with atherosclerosis and the metabolic syndrome. The CTMM PREDIICCt consortium (Biomarkers for the Prediction and Early Diagnosis of Diabetes and Diabetes related Cardiovascular Complication, principal investigator Martin Hofker) was created to build on the latest insights into the etiology of Type 2 Diabetes Mellitus (DM2), and to develop innovative biomarker-based technologies to enable the identification of individuals at increased risk of DM2 and DM2 related complications. DM2 can be predicted quite well with existing simple biomarkers (e.g. weight and plasma markers). The challenge is to increase our understanding of metabolic programming as a novel source of biomarkers, to complement existing genetic markers. Within the PREDIICCt program, high fat diets given to rodent model mothers during pregnancy and pre-weaning increased their offspring's susceptibility to fatty liver disease and metabolic syndrome. The model allowed searching for suitable imprinting biomarkers such as DNA methylation markers, histone modifications and others. These markers can be detected in peripheral blood and may occur before the onset of obesity. As such, they offer an opportunity to develop an early test that can be used in combination with genetic information to offer lifestyle advice.

As is the case for many other diseases, diabetes is multifactorial in origin. In Upstate, there is no single root cause of the disease. Moreover, many of the disabling effects of the primary disease are related to complications downstream of the primary disease, and the patient's quality of life may also be more impaired by these complications than by the disease itself. Vascular complications related to diabetes are one such example. The ability to calculate a patient's risk of developing complications, and the ability to detect or monitor these complications at an early stage, would be an important asset to manage and control their treatment and monitor the effect of lifestyle improvements to reduce complications. From 31 tested markers, the PREDIICCt consortium identified 13 biomarkers that were able to improve the prediction of vascular complications by between 15% and 20%. As a consequence, these tests resulted in a 6.6% reduction in the number of patients receiving intensive treatment, while not affecting the overall burden of vascular complications in the study population. The tests were developed using large existing cohorts, including the EPIC-NL cohort (the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition study), with a total of over 40,000 men and women aged 20-70 years at recruitment during the period 1993 to 1997. The purpose of the EPIC-NL study was to assess the relationship between nutrition and cancer and other chronic diseases. Another large study included in the program was the SMART (Second Manifestations of ARterial diseases) cohort, an ongoing, prospective, single-center cohort study of patients with cardiovascular risk factors or clinically manifest arterial diseases. SMART includes over 8,200 patients with more than 10 years of follow-up. In addition to these large population-based studies, which will contribute to a better understanding of the aetiology of diabetes, the PREDIICCt consortium worked on two new early Warning devices that can be used to measure an individual patient's risk of developing severe complications from diabetes. The first device is the so-called Glycocalyx Measurement System.
The glycation is a gel-like coating on the luminal surface of blood vessels, and structural changes to it is one of the earliest signs of atherosclerosis. The measurement system analyzes video recordings of the blood flow to assess whether a patient is at risk of either condition. The correct flow of blood to organs and tissues is key for our health and well-being. Haemorrhage and thrombosis in-vivo or in-vitro both compromise blood flow and can be the threatening events that require urgent action. At present, however, there is no convenient test available for assessing whether a patient is at risk of either condition.

The INCLUDA consortium (Innovative Coagulation Diagnostic, principal investigator Hugo ten Cate) represented an unique consortium to collectively improve coagulation diagnostics. The ultimate goal was to establish new diagnostics tests that better detect the risk of haemorrhages and thromboses, and that could also be used to monitor the effect of anti-antithrombotic drugs.

One of the outcomes of the program was a point-of-care device (Thrombin Generation Assay) that can be used to determine if there is a need for surgical surgery to assess their risk of serious bleeding associated with the surgical intervention.

This simple desk-top device measures haemostasis by assessing the thrombin generated quickly and accurately using a small-volume whole blood sample – for example, a finger prick sample. In the mean time, this activity has materialized in the creation of an expert center for thrombosis and hemostasis.

Another non-invasive medical device that was optimized and tested in the PREDICCt project and subsequently commercialized is the AGE Reader – an optical system that productized is the AGE Reader – an optical system that assesses the level of Advanced Glycation End-products (AGEs) in the dermis of a patient’s skin. Increased AGE levels in the dermis have been demonstrated to be a strong, independent predictor of cardiovascular and serious complications.

The CTMM DeCoDe program (Decrease Colorectal Cancer Death, principal investigator Gerrit Meijer) addressed this unmet clinical need by developing a better screening test for CRC. In addition to developing a better screening test for CRC, other research in the DeCoDe program resulted in the discovery of a DNA methylation marker that predicts response to the anti-cancer drug irinotecan, and image-guided surgical procedures to treat CRC liver metastases.

In vivo molecular diagnostics in Alzheimer’s disease prevention relies heavily on early detection. But unfortunately, there are many diseases for which effective remedies are either completely lacking or in their infancy. However, even for diseases where there is no treatment, early detection is still important. It may, for example, provide surrogate markers that can be used to expedite the testing of new treatment regimes. It may also help to anticipate the progression of a disease so that timely advice on lifestyle can be given and support structures put in place.

The high-potential protein biomarkers developed in the project are currently being validated in a controlled study using colonoscopy material as part of the CTMM CRCDiagnosis project – a validation study that was created by CTMM to further improve the sensitivity and specificity of the test currently being used in the Netherlands’ large-scale CRC screening program. The less then than serenity of current CRC screening tests means that around 30% of CRCs and the majority of high-risk precursors are not currently identified by screening. Better serenity and specificity – in simple terms a better hair – are absolutely required to make a major step forward in the prevention of death by colorectal cancer. This is where the DeCoDe program will have its greatest impact.

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A typical example is the early detection of patients suffering cognitive decline due to Alzheimer Disease (AD). In 2005, the Dutch National program focused on in vivo molecular diagnostics in Alzheimer Disease – Leden-Alzheimer Research Foundation (principal investigators: Mark van Buchem and Bart van Berckel) developed new imaging techniques (MRI and PET) to visualize specific ‘tangles’ in the brains of AD patients, as well as glial/neuron/otherochrome and the associated receptors to which they bind. The project consortium also developed technologies that can be used to identify and quantify biomarkers for AD in cerebrospinal fluid.

Keeping blood flow under control – the risk for bleeding and thrombosis

The CTMM DeCoDe program (Decrease Colorectal Cancer Death, principal investigator Gert Meijer) addressed this unmet clinical need by developing potential new stool DNA and protein biomarkers and a new PET imaging tracer for screening applications.

Through improvements and the early assessment of risk, caregivers, patients, and their families can detect disease in its very early stages, before it becomes malignant.

Lifestyle improvements and the early assessment of risk, caregivers, patients, and their families can detect disease in its very early stages, before it becomes malignant.

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The high-potential protein biomarkers developed in the project are currently being validated in a controlled study using colonoscopy material as part of the CTMM CRCDiagnosis project – a validation study that was created by CTMM to further improve the sensitivity and specificity of the test currently being used in the Netherlands’ large-scale CRC screening program. The less then than serenity of current CRC screening tests means that around 30% of CRCs and the majority of high-risk precursors are not currently identified by screening. Better serenity and specificity – in simple terms a better hair – are absolutely required to make a major step forward in the prevention of death by colorectal cancer. This is where the DeCoDe program will have its greatest impact.

In addition to developing a better screening test for CRC, other research in the DeCoDe program resulted in the discovery of a DNA methylation marker that predicts response to the anti-cancer drug irinotecan, and image-guided surgical procedures to treat CRC liver metastases.

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That’s how Bob Löwenberg, principal investigator of the CTMM BioCHIP consortium commented Bob Löwenberg. "Diagnosis in leukaemia, an art of distinction”

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From an analysis of these datasets it became clear that in addition to traditional cytogenetic aberrations, novel genomic signatures also were developed. These signature-driven diagnostic tools were validated in several independent clinical cohorts. Several other genomic signatures were also developed, with those that were major drivers of these findings being so-called copy number alterations (CNAs). These CNAs were predictive of overall survival, which has now been validated in six independent clinical cohorts. Several other genomic signatures were also developed, which included extensive CT, MRI and ultrasound imaging of the coronary arteries. A centralized platform for data storage, analysis and quantification enabled the development and validation of novel imaging analysis tools. Several scientific papers have been published in the design of the PARISk clinical study and a cross-sectional analysis of the imaging data taken after inclusion of the first 100 patients. Methods for candidate biomarker selection based on predefined clinical selection criteria (e.g. MACE = major cardiovascular events).

The CTMM PARISk consortium (Assessment of Plaque at Risk by Non-invasive (Molecular) Imaging and Modelling, principal investigator Maaike Daezen) addressed the problem of identifying high-risk patients with symptoms that often only appear in very late stages of disease development. People with risk factors such as diabetes, high blood pressure, hypercholesterolemia, smoking and obesity all have increased risk factors of suffering from severe symptoms at a younger age. Clinical manifestations associated with atherosclerotic disease progression include myocardial infarction, stroke and peripheral artery disease.

Atherosclerosis can progress very slowly over decades, without warning signs or symptoms. A patient may not be the cancer with the highest impact on the situation in which a patient's whole genome will be assessed in a single assay, for example via the use of microarrays and next-generation sequencing or high-throughput genotyping systems. To prevent atherosclerosis, it will remain a major risk for cardiovascular events such as an acute myocardial infarction and stroke are caused by rupture of a vulnerable so-called atherosclerotic plaques – abnormal deposits of "omic" and "non-omic" results were used with different peripheral artery disease.

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A panel of medical technology assessment experts have completed an analysis of current practice and costs for the diagnosis and treatment of patients with cardiovascular disease, and have now optimised their models to evaluate the effect of the PARISk multimodal imaging approach. This analysis is based on the CTMM TRACER consortium multimodal imaging approach for the diagnosis of symptomatic cardiovascular disease, which was completed four years after the PARISk consortium, has been very successful in generating new imaging parameters for the risk assessment for patients with cardiovascular disease as a hallmark for the fatal progression of the disease as well as for the transition between potential success and failure of therapy. For this purpose, multiple diagnostic technologies were developed to enable the early detection of neovascularization, and novel tools were developed to stratify on an individual patient’s risk of cardiovascular disease. To accelerate their transition into clinical practice, the project designed prototypes to synthesize molecular markers and label them with radiolabel or isotope and/or ultra-miniaturized devices for use in combination with PET/CT/SPECT imaging. In addition to these imaging approaches, the project improved functional MRI imaging in order to assess the perfusion consequences of neovascularisation by optimizing flow measurements for small arteries and quantifying cardiac and skeletal muscle perfusion.

Another disease in the cardiovascular domain where risk assessment will have a major impact on patient management is heart failure (HF) – a progressive condition with a very adverse impact on patients and society. Heart failure varies in nature from a chronic progressive disease, benignly progressing disease to an aggressive malignant disease in which patients can deteriorate quickly. However, a major shortcoming of current heart failure management is the inability to predict which patients need more aggressive treatment. The major reason for this is the identification of more than 20 novel biomarkers related to heart failure, all of which have a biological role in the disease, and are largely asymptomatic and a prognosis, in terms of disease progression, established. To meet this need, the TRACER consortium developed a diagnostic test for the identification of preclinical VERA and a prognostic algorithm to predict its progression that combines the interferon gamma predictor gene signature with other clinical data. This test has now undergone CE-certification and is being developed for possible marketing in the coming years.

Rheumatoid Arthritis – a matter of timing

Rheumatoid arthritis (RA) is a heterogeneous disease in which inflammation leads to irreversible joint damage, with consequent disability and severely impaired quality of life. The onset, nature, and rate of progression of joint damage and response to therapy are different for each patient. Making the right treatment decision at the right time is critical to the patient outcome. Unfortunately, current tools for diagnosis, prognoses, and treatment selection are both limited and sub-optimal. This was the topic addressed by the CTMM TRACER consortium (TRACER: Towards an Effective Early Arthritis Screening Tool) that combines the interferon gamma predictor gene signature with other clinical data. This test has now undergone CE-certification and is being developed for possible marketing in the coming years.

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This prompted the consortium to translate these laboratory findings to the patient setting by developing a novel breath-test tool that could essentially be used as a point-of-care device to assay the identified biomarkers. So what was essentially a biomarker discovery project has resulted in a next-generation of health device to monitor the risk of severe heart disease progression in individual patients.

As an important side effect, the search for diagnostic biomarkers has also resulted in a candidate target for a new therapeutic, as the cytokine p40 was not only significantly expressed in HF patients but is also shown to be upregulated in RA patients. This opens the potential of developing innovative new treatment to intercept inflammation in HF as well as in RA (where p40 is known to be upregulated). The result was the identification of more than 20 novel biomarkers related to heart failure, all of which have a biological role in the disease, and are more importantly, can be measured in patients.

There is ample evidence that the timing of intervention, either in terms of prevention or slowing down joint damage, is critical to the patient outcomes. Unfortunately, current tools for diagnosis, prognoses, and treatment selection are both limited and sub-optimal. This was the topic addressed by the CTMM TRACER consortium (TRACER: Towards an Effective Early Arthritis Screening Tool) that combines the interferon gamma predictor gene signature with other clinical data. This test has now undergone CE-certification and is being developed for possible marketing in the coming years.

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By enabling the design of personalized RA treatment strategies, the costs associated with unnecessary RTX administration are reduced and patient health outcomes improved. A commercial partner from abroad that specializes in host biomarker assays is interested in further development and production of the kit-based RT-PCR assay to achieve market access.

The quality of RA research in The Netherlands is well recognized and attracted substantial attention (and support) from private partners when the TRACER consortium was founded. As described above, one developed test has passed CE certification and will hopefully reach the market soon. Other findings include specific PET tracers, X-ray reading software, ACPA profiles and gene sets that may all have a place in patient tailored treatment. It is also worth noting that the core members of the TRACER consortium have already rejoined forces in the follow-up MODIRA program (Molecular Diagnostics in Rheumatoid Arthritis, principal investigator Dirkjan van Schaardenburg).

Do no harm … how to prevent overtreatment

One of the ground rules in medicine is ‘first do no harm’ (Primum non nocere). This may seem obvious, but with more diagnostic tools at our disposal there is always the risk that we will over-treat. Sensitive tests are great for the early detection of disease, but may be dangerous if they lack the specificity to avoid large numbers of false positives. Prostate cancer is a major cause of death for men in the Western world. It can be treated by radiotherapy or surgical removal of the prostate, but a substantial number of patients suffer relapses due to metastatic foci, for which only palliative therapy is available. The CTMM PCMM project (Prostate Cancer Molecular Medicine, principal investigator Chris Bangma) has addressed the major clinical need for a test with greater specificity through a multi-disciplinary consortium composed of academic hospitals, biomarker and imaging research groups, and diagnostics and pharmaceutical companies.

One of these tests, SelectMDxTM, addresses the unmet need for stratification of patients into those at risk for potentially lethal high-grade prostate cancer and those with low-grade prostate cancer. This non-invasive urine test has a higher specificity for clinically significant prostate cancer than the currently used prostate specific antigen (PSA) test. By reducing the number of false positives it reduces patient anxiety levels and unnecessary invasive prostate biopsies, together with the associated risk of co-morbidity. It therefore has the ability to significantly reduce overtreatment. At the same time, it identifies those men at increased risk of harbouring high-grade disease who may benefit most from early detection.
Treatment Prediction

For years, the Holy Grail in medicine has been to find the single pill or intervention that permanently cures the patient. New medicines have reached the market and a large number of new medical devices and surgical procedures have been developed. However, despite this progress, we often have no clue about which patient should receive which (new) treatment, and how aggressively we should treat. Overtreatment is an often-heard complaint by healthcare policy makers but that clearly does not mean we should undertreat. Reducing patient discomfort and anxiety and mitigating escalating costs will require better and faster diagnostic tools to determine which treatment options really fit the widely acclaimed P4 (Predictive, Preventive, Personalized and Participatory) model of medicine.

Sepsis …

the most common cause of death in hospitals

Globally, sepsis causes millions of deaths each year. It is the most common cause of death in people who have been hospitalized. Until very recently, the prevailing concept in the pathogenesis of sepsis was that mortality is the consequence of an uncontrolled hyper-inflammatory host response. The disappointing results of nearly 40 years of anti-inflammatory treatment strategies have led to a reconsideration of the pathophysiology of sepsis. Although the possible reasons are numerous, a major factor contributing to the failure of so many clinical sepsis trials probably lies in the heterogeneity of the patient cohort, which stems from the lack of tools for effective classification of each patient’s immune status and the corresponding medical decision-making. Currently available tools for therapy selection and management comprise symptom classification systems and conventional microbiological techniques. The former are only validated for outcome predictions in large populations, not for individual patients, and the latter have low sensitivity and a typical diagnostic delay of at least 24 hours, during which time sepsis can lead to irreversible multiple organ failure.

To address the complexity of the sepsis response and predict its outcome, multiple surrogate markers that reflect the nature and severity of the inflammatory response and the magnitude of organ injury are likely to be more effective in identifying patients at risk of an adverse outcome who may benefit from interventional therapies. Such strategies will inherently require the use of multiple approaches that provide insights into a patient’s inflammatory and immune status. The gene-by-gene or protein-by-protein approach may be rendered obsolete by these requirements.

The CTMM MARS consortium (Molecular Diagnosis and Risk Stratification of Sepsis, principal investigator Tom van der Poll) generated tools that provide rapid and accurate information about which microorganism is responsible for an individual patient’s infection, and the severity and stage of the patient’s immune response.
These tools are easy to use, at or close to the patient’s bedside, and provide rapid information that helps clinicians treat each individual patient in the best way. Time is therefore of utmost importance to save lives and reduce health care costs. The MARS project generated an almost 7000 ICU patients, combined with a very large unprecedentedly large and rich database covering susceptibility analyses in order to stratify sepsis patients into more homogeneous subgroups, allowing more comprehensive process control. The two companies will work closely together to launch the system commercially in the EU and US.

Rapid and accurate information is crucial in treating sepsis and fungal pathogens within 2 hours of taking a blood sample. The MARS project that detects the most relevant bacterial and fungal pathogens within 2 hours of taking a blood sample was also developed in this project. The consortium members are fully committed to continued collaboration, not only in accordance with the MARS deliverables but also beyond the objectives listed in the project proposal. They have already made plans for further validation to validate some of the tools developed in MARS, and new projects such as prokinease and genetic susceptibility analyses in order to stratify sepsis patients even more homogeneously, allowing more individualised therapy. The value created in the MARS project is enormous and sustainable in the future. It can now be used as a platform for global research questions, for validation of novel diagnostic tools, and for altering the existing market valuation of new products.

Looking for the beneficiaries of anti-arrhythmia therapy

Cardiovascular diseases, congestive heart failure (CHF), arrhythmia, and myocardial infarction are the principal investigator Mark Vos) aimed to develop a binding protein to image fibrosis in animal models, CXADR (Coxsackie Virus And Adenovirus Receptor) were developed and tested include the protein coding for the CXADR protein. Genetic, blood borne and ecological factors may give rise to cardiovascular disease. Biomarkers that will help to identify patients who have a high risk of cardiac arrhythmias, including atrial fibrillation (AF), and biomarkers that will help to identify patients who have a high risk of cardiac arrhythmias, including atrial fibrillation (AF). For example, around 65% of ICDs are never activated during their battery lifetime, and around 35% of patients with a CRT implant do not respond well to it. Therefore, there is a need to better homogenise subgroups but to develop early diagnostic tools to screen and stratify patients before these therapies are applied.

The CTMM COHFAR project (short for predict cardiac arrhythmia, arrhythmia, and myocardial infarction) aimed to develop an ECG-based algorithm and non-invasively classify AF and guide therapy. Clinical and research performed in this program aimed to identify and markers And Response to CRT, primary MARC study (Neoadjuvant Drug Treatment for Breast Cancer Response Prediction and Response Monitoring) in 50% of HER2/neu positive tumors. The optimal neoadjuvant treatment regimen is unknown, and is almost certainly different for each individual tumor.
molecular imaging. Of these modalities, PET is by far the level – i.e. molecular imaging. Optical, MRI and resolve and study human metabolism on a molecular existing in both lung and head-and-neck cancer, which gene-expression patterns. These results suggest that intra-tumor heterogeneity was strongly prognostic in example, it is known that tumor cell metabolism, proliferation and angiogenesis are capable of demonstrated that certain drugs directed against targets individual tumors differ in their sensitivity to treatment. For example, PET imaging is based on the use of radioactive tracers PET tracers are of definite value for predicting and within the CTMM AIRFORCE consortium (targeted) drug for this selection of right uptake lymphoma on PET-CT something that was clearly demonstrated in the CTMM Imaging makes ‘personalized medicine’ possible Researching for a universal vaccine that does not require yearly vaccination...
Cancer diagnosis has improved tremendously due to the development of non-invasive imaging technologies such as PET, SPECT, CT and MRI. By accurately delineating tumors, these imaging technologies allow tumors to be removed using open surgery or minimal-invasive techniques such as laparoscopy. In malignant diseases such as cancer, it is of paramount importance that the target lesions are removed completely with sufficient tumor-free margin. During surgical procedures, discrimination between tumor and normal tissue is difficult. This is especially true during laparoscopic surgery, where deprived of the tactile information obtained via palpation, the surgeon has to rely on image guidance.

To provide the surgeon with additional information during a laparoscopic procedure, optical fibers for spectral analysis of specific tissue regions and a miniaturized biopsy device that can remove a tissue sample from these regions were developed. To visualize tumor cells, two near-infrared fluorescent (NIRF) imaging probes (the EPICA-CW800 and RGD-ZW800) were developed. Both probes are currently being produced under GMP conditions and clinically tested. The availability of these new tumor targeting NIRF probes and the multispectral NIRF camera systems for image-guided surgery make it possible to visualize tumor tissue in real-time with high precision and sensitivity. The camera systems can also be used for the recognition of sentinel lymph nodes using non-targeted NIRF probes. With the translation of targeted probes to the clinic, image-based intraoperative identification of new tumor margins and location may enable microsurgery to be performed and the percentage of radical tumor resections is expected to be increased.

This makes accidental non-radical resection, a serious clinical problem. The CTMM VOLTA project (Magnetic Resonance guided High Intensity Focused Ultrasound) is the only known technique capable of completely non-invasively controlled thermal ablation, because it not only allows ultrasound guided HIFU heating deep inside the human body. Up until now it has been used primarily for the treatment of prostate cancer, guided by ultrasound imaging. However, when using ultrasound guidance, 3-dimensional information is frequently lacking and accurate temperature mapping is not possible. In contrast, MRI is well suited to HIFU guidance, because it not only allows continuous imaging of the tumor and the surrounding healthy tissue, but can simultaneously be used to acquire 3D temperature maps inside the patient. Such maps can be used to control the heating procedure, so that the tumor is adequately heated. The combination of MRI and focused ultrasound is called MRI-guided HIFU (Magnetic Resonance guided High Intensity Focused Ultrasound). In the VOLTA project, dedicated MRI-guided HIFU technology was developed for treating breast cancer and metastases in the liver completely non-invasively, an approach that may ultimately replace surgery for these tumors.

Proof-of-concept of MRI-guided treatment of breast cancer including validation of treatment and monitoring protocol has been obtained in a selected number of patients. The results show that MRI-guided HIFU is safe and results in histopathologically proven tumor necrosis. A Phase II clinical study is IRB approved and will be performed in a subsequent program that has been granted a transition grant to further validate and scale-up this new treatment.

Thermal Ablation, principal investigator (Dirk Nooter) and HIFU (High Intensity Focused Ultrasound), principal investigator (Dirk Storm) projects. The VOLTA consortium’s research was based on the principle that it is possible to tranfer ultrasound into a patient in such a way that the acoustic energy primarily ends up in one location (the focal point) where it can locally heat tissue to a temperature that kills tumor cells – a process called thermal ablation. The possibility of locally heating tissue without doing harm to surrounding tissue opens a pathway towards new therapeutic strategies with improved reliability and less associated toxicity, potentially resulting in improved efficiency, reduced periods of hospitalization, reduced treatment costs and improved quality of life. High Intensity Focused Ultrasound (HIFU) is the only known technique capable of completely non-invasively controlled thermal ablation, because it not only allows ultrasound guided HIFU heating to make the tumor body. Up until now it has been used primarily for the treatment of prostate cancer, guided by ultrasound imaging. However, when using ultrasound guidance, 3-dimensional information is frequently lacking and accurate temperature mapping is not possible. In contrast, MRI is well suited to HIFU guidance, because it not only allows continuous imaging of the tumor and the surrounding healthy tissue, but can simultaneously be used to acquire 3D temperature maps inside the patient. Such maps can be used to control the heating procedure, so that the tumor is adequately heated. The combination of MRI and focused ultrasound is called MRI-guided HIFU (Magnetic Resonance guided High Intensity Focused Ultrasound). In the VOLTA project, dedicated MRI-guided HIFU technology was developed for treating breast cancer and metastases in the liver completely non-invasively, an approach that may ultimately replace surgery for these tumors.
Collectively, these examples of prevention, prognosis, treatment prediction and guidance span the entire cycle of care. From pre-emptive to curative medicine, from simple point-of-care solutions to advanced imaging and next-generation sequencing platforms, from large-scale population-based studies to personalized treatment. The individual players – the talented researchers, world-class academic medical centers, established industries, entrepreneurial SMEs – were all present in the Dutch life sciences eco-system, but it was the CTMM program that combined those creative forces, made them work together, and produced a wealth of data sets, scientific papers, well-trained young scientists and, most importantly, new healthcare solutions for myriad patients suffering from a broad spectrum of diseases. And last but not least, CTMM created TraIT (Translational Research Information Technology) platform – an IT infrastructure for data sharing and interoperability in translational research.

Since the very early days of CTMM, IT experts from all the consortia were brought together to create a consensus about the most optimal IT tools for assembling connecting the public and private partners. It quickly and painfully showed that many of the existing tools at the time were far from optimal or even useless when it comes to true collaboration in the translational research setting. CTMM was confronted with a melting pot of preclinical and clinical research IT needs, at least 6–8 core data sets, wide-spread patient information, and clinical and non-clinical data from imaging and pathology labs. A Babylonian confusion of tongues was the result. Together with (co-author) Gerrit Meijer, pathologist and principal investigator of the CTMM DeCoDe project, CTMM made a quantum leap and created TraIT.

The name of the game became: ‘Think big, start small, act now’, rather than trying to come up with a holistic approach that attempted to solve all the IT issues in a uniform way, a bottom-up approach directed to the actual needs of translational researchers working at the interface of different disciplines and institutions was adopted. To kick-off the idea, CTMM contacted similar initiatives such as the National Cancer Institute in Bethesda, adopted best practices, and started implementing a platform that can now be adopted for the integration of huge, diverse datasets for the ultimate goal of personalized medicine. TraIT enables integration and querying of information across the four major domains of translational research: clinical, imaging, biobanking and experimental (any-omics) with a particular focus on the needs of multi-center projects. Rather than embarking on a major software development program, TraIT has a clear preference for proven technology that can be adopted or adapted to the specific needs of translational research projects. Both the Dutch Heart Foundation (NHS) and Dutch Cancer Foundation (KWF) contributed substantially to the program as they immediately understood the unmet need for which TraIT offered a solution. While continuing to extend its services, TraIT has already supported over 250 research projects and over 2500 individual researchers. The backbone of this program has been extended by other national initiatives, such as the NBO (Dutch Federation of Academic Hospitals) Data4Life Sciences program and BBMRI-NL, the Dutch node in the European biobanking network. TraIT has become and continues to be the fundamental support structure for many translational programs in the Dutch life sciences, and has recently extended its operations to serve international (European) molecular medicine programs as well.
Patient outreach, participatory medicine

Crossing the translational ‘valley of death’ to create healthcare solutions and products that will impact the diagnosis and treatment of real patients is one of the greatest challenges in modern medicine. Public-private partnership translational research is one way of expediting the market introduction of these new solutions, but in the ‘digital age’ there are other ways of disseminating scientific knowledge and putting useful tools in the hands of healthcare professionals and patients. Within the CTMM AIRFORCE project, MAASTRO Clinic (Maastricht) developed a set of computer models designed to predict the outcome of different treatment options for a range of cancers – including lung, rectal, head & neck and endometrium cancer.

To get them into the hands of cancer specialists as quickly as possible, it made them freely available on the www.predictcancer.org website, allowing clinicians to enter parametric data for a specific patient and receive outcome predictions for different treatment options. Having put this powerful clinical decision support tool into the hands of clinicians, many research groups would have stopped there – job done. However, Philippe Lambin at MAASTRO Clinic and his team also knew that choosing the right treatment for the right patient was not a clear-cut decision. Different treatments have different side effects, so more often than not, the final choice of treatment requires a dialogue between physician and patient. His team therefore set up a parallel website called www.treatmentchoice.info, to provide patients with information on different treatment options and help them to pinpoint what is important to them. Patients benefit from being better informed, clinicians benefit from improved patient feedback and the ability to identify patient groups that might benefit from specific treatments. That’s how participatory medicine should be practiced.

Detailed information on all the results achieved in the CTMM program can be found in project booklets on www.ctmm.nl.
Scientific impact

Project proposals submitted for CTMM funding were subjected to (international) peer review, plus assessment by the CTMM’s International Scientific Advisory Committee (ISAC). Two calls for proposals were used to select the majority of the projects, while a joint call with Ti Pharma and BMM invited proposals for additional projects in the area of ‘Imaging Guided and Targeted Drug Delivery’. Towards the end of its program, CTMM also awarded valorization grants to selected consortia that were close to bridging the gap between fundamental research and value creation. A minimum of 3 international experts, including one Health Technology Assessment specialist, undertook the initial review of every proposal. The final ranking of the projects was then performed by the experts, including one Health Technology Assessment specialist, undertook the initial review of every proposal. The final ranking of the projects was then performed by the ISAC. Based on this ranking, the CTMM Supervisory Board approved selected project proposals.

One of the most important goals of the CTMM program was overcoming the ‘valley of death’, bridging the gap between fundamental science and its translation into clinical and economic value. Public-private interactions are an important instrument to achieve this. As a result of the mid-term reviews, each of which involved a detailed oral presentation by the project’s principal investigator, the most promising lines of investigation from a translational point of view received additional support to reinforce and expedite them at the expense of less promising research. The ISAC did not rely solely on the presented information. It also found the facilities of many CTMM consortia members to discuss specifics of the projects on site.

One of the most important outcomes of the CTMM program was the establishment of a pan-European network of medical imaging experts and IT experts from outstanding research institutes around the world, the ISAC embodied a broad spectrum of expertise both in fundamental science and its translation into healthcare solutions and products. The network was decision, both in selecting the best projects and in the mid-term reviews to which all projects were subjected. As a result of the mid-term reviews, each of which involved a detailed oral presentation by the project’s principal investigator, the most promising lines of investigation from a translational point of view received additional support to reinforce and expedite them at the expense of less promising research.

The ISAC did not rely solely on the presented information. It also found the facilities of many CTMM consortia members to discuss specifics of the projects on site.

This is all the more so because scientific excellence was both the starting point of all CTMM projects and a key indicator of their performance. It is a misconception that clinical research is only about basic science. Public-private partnerships are very important but they are not a panacea, and they will always be founded on basic science that has been developed independently of clinical research. Public-private partnerships are very important but they are not a panacea, and they will always be founded on basic science that has been developed independently of clinical research.

During the CTMM round table discussions that took place in Utrecht in November, 2014, ISAC-member Jan Andersson from the Karolinska institute in Stockholm, stated that by capitalizing on all medical centers in the Netherlands, CTMM was a unique construction for stimulating excellent clinical trials, translational research in colorectal cancer was typically centered round individual PIs with one PhD student. With CTMM, he considered that colorectal cancer research had come to be treated as a single entity, and that the Dutch Colorectal Cancer Group was addressing this gap in a different way. He also pointed out that prior to CTMM, translational research started with basic science. Public-private partnerships are very important but they are not a panacea, and they will always be founded on basic science that has been developed independently of clinical research. During the CTMM round table discussions that took place in Utrecht in November, 2014, ISAC-member Jan Andersson from the Karolinska institute in Stockholm, stated that by capitalizing on all medical centers in the Netherlands, CTMM was a unique construction for stimulating excellent clinical trials, translational research starts with basic science. Public-private partnerships are very important but they are not a panacea, and they will always be founded on basic science that has been developed independently of clinical research.
In terms of scientific output, a total of 237 PMID entries have been successfully compiled as a result of the CTMM project. By the beginning of 2012, 709 papers have been published, most of them in peer-reviewed journals with impact factors similar to those of more traditional academic research publications in similar subjects areas, and approximately 270 are still prepared for submission. In addition, two CTMM researchers have been awarded ERC grants, and virtually all of the programs have been able to acquire subsequent financial support from national or European funding agencies to continue their research.

The ISAC is in the process of keeping the scientific standard of CTMM research ‘second to none’, but its other very important contribution was starting the programs to go the ‘virtual’ route, creating the clinical or economic value that CTMM aimed at from the beginning. While the ISAC helped to ensure scientific excellence, it was highly professional program management by the CTMM program managers that facilitated the necessary cooperation and kept the programs on track.

In terms of scientific impact, another important aspect of CTMM has been its emphasis on the sharing and exchange of scientific data between scientists in different institutions and companies. As a result, a number of highly valuable clinical data collections have been created that will serve as extremely rich sources in subsequent research activities for years to come. The CTMM program sponsored many researchers, for the third time in their careers, to large multi-disciplinary collaborations in which data and new scientific results were shared among colleagues from different R&D sites in academia and industry settings. This is highly significant, because innovation frequently finds its origins at the interface of different disciplines. CTMM has thus aimed at creating a scientific and knowledge-sharing structure that fosters innovation, in particular in the context of the early-stage research.

The forkhead box O (FOXO) family of transcription factors serves as key regulators of survival and metabolism and plays a critical role in aging5. FOXOs are members of a larger family of orthologous genes and are known not only to share a conserved domain structure but also to have distinct expression patterns and functions5. FOXO family members include FOXO1, FOXO3, FOXO4, FOXO6, and FOXO11. These genes are expressed in many tissues and play a role in the regulation of gene expression, which is induced by growth factors, insulin, and hormones5. However, specific functions of particular FOXOs have been described, which in part can be ascribed to their tissue-specific expression (for example, FOXO6 is known as AKT and c-AKT); and FOXOs are activated via serine phosphorylation, mediated by Akt and c-Akt6.

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Translational Research and Medical Technology Assessment (MTA)

It has been stated that a time lag of 17 years for research evidence to reach clinical practice is more the rule than the exception. The two main challenges for CTMM were translating excellent science into diagnostic solutions that will have an impact on health and wellbeing, and do it with better yields and shorter lag times than before.

It should come as no surprise that the duration of the CTMM program – just five years – was too short a time horizon for all the ideas generated in the CTMM projects to be turned into on-the-market clinical solutions. Nevertheless, with 26 patent applications, 7 new SME spin-offs from the academic medical centers, and more than 147 new diagnostic devices either prototyped or produced, CTMM has proven that accelerating the pace of translational medical research is not only feasible but doable. And those numbers only represent the ‘lower hanging fruit’ in the CTMM program. With the benefit of valorization grants from CTMM and supplementary transition grants from the Dutch government, many more high-potential CTMM projects remain on track to deliver clinical solutions and products. 1

Examples in the oncology domain are the CRCbioscreen project, which is developing a next-generation screening test for colorectal cancer based on tumor-specific protein biomarkers in stool samples; the Nano CA-IX project, which is developing a molecular imaging technique to detect alterations in (breast) tumor cells that may provide new windows of opportunity to treat hypoxic tumors; CHOICE, a computer-aided prediction of breast cancer therapy response by means of multimodality imaging; the VOLTAVALO project, which is performing a Phase II clinical trial on MR-guided focused ultrasound ablation of breast tumors; and the PROCAMOLMED project, which is validating two novel molecular markers for prostate cancer. While some of these high-potential projects are straightforward follow-ons, other programs have cross-linked their research efforts to create new projects. For example, the NGS-ProToCol project, which aims to identify diagnostic and prognostic biomarkers for prostate and colorectal cancer using next-generation sequencing technology, is a new valorization project that builds on the results of work packages in the PCMM and DeCoDe projects.

In the cardio-vascular disease area, the ECAF project is in the final stages of developing a tool for the non-invasive classification of atrial fibrillation (AF) using AF complexity analysis of the oesophageal electrogram; the ENGINE valorization project is continuing development of a next-generation multiplex miRNA assay for heart failure that was developed in the TRIUMPH project; and
All these follow-on initiatives focus on the translation of the new MARS&MORE program is capitalizing on earlier CTMM program research results into practical products or clinical procedures. They are of earlier CTMM program research results into practical products or clinical procedures. They are.

Medical health-economic modeling typically uses a 4-step approach:

1. Analysis of how the new technology will be applied in patient care, the target population, and the outcome measurement.
2. Description of current care for the defined population as the base-case comparator for MTA analysis.
3. Description of proposed care for the defined population using the new technology.
4. Analysis of the cost-effectiveness of the proposed care to establish the minimum required performance of the new technology to make it viable alternative in actual clinical practice.

In the Early MTA approach adopted by CTMM, these steps have been initially performed in the technology development phase and refined right through to the product development phase. As stated by Kurt Paap and Diederik Sturkenboom, both MTA experts involved in the MICRO-BAT and PREBAT projects, two follow-on initiatives of the INCOAG program, are developing a microscope-independent thrombus formation assay to validate bleeding and thrombosis risks, and validating a new single blood drop test to assess thrombin generation respectively. The Tailor-CRT valorization project will combine cardiac motion imaging and cardiac testing technology to assess the ability of vector cardiograms to assess resynchronization and hence improve insulin resistance and vascular function in obese patients. And in the area of infection, the PREDICCt project to detect advanced glycation endproducts (AGEs) as a marker for diabetes, using endproducts (AGEs) as a marker for diabetes, using pyridoxamine to interfere with the accumulation of AGEs has the potential to substantially improve the outcomes of patients with diabetic complications.

MTA will not simply be used by reimbursement authorities once a technology is still in (early) development. This means that results of the MTA must be available prior to the implementation of the new technology in actual clinical settings.

However, it has become increasingly clear that cost-effectiveness is not the only issue. Medical, social, ethical and societal value is also important. From both the research funding and commercial investment perspective, it is therefore worthwhile determining the feasibility of applying MTA tools in the early stages of biomedic product development to rationalize further development and anticipate market access. Figure 1 illustrates the different stages, early and classical of the MTA cycle.

In the early stages of technology development, health-economic modeling cannot be a powerful tool for assessing the impact of a new technology on future healthcare costs and outcomes. Drawing on different sources of information, a valuable exploration of the potential costs and outcomes associated with alternative ways of using a new technology in clinical practice.

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Developed in collaboration with other Dutch initiatives and CTMM partners in the Life Sciences and Health sector, CTMM’s comprehensive Education and Training program aimed to bridge the cultural differences and knowledge gaps between academic and industrial research. Special attention was given to aspects not typically covered by Masters Degrees or PhD curricula in the Netherlands’ medical schools and universities.

Courses were run on the following topics and wherever possible included role-play exercises to give course participants hands-on experience of the topic being discussed.

**Intellectual Property**
Creating awareness of Intellectual Property (IP) issues in life-science research, such as how to identify, protect and manage new inventions.

“To me the most important message of the IP-course was that protection of your Intellectual property in patient applications is as important as publishing your results in articles, even if you are working in an academic environment.” - A. Post, Postdoc, VUmc Amsterdam

**Translational Research Simulation**
Providing insights into the complex issues involved in transforming a novel idea into a valuable product via a practical case study.

“Step into a helicopter and fly from the biological development of a biomarker to its adoption on the healthcare market.” - R. Hendrix, PhD Student, MUMC Maastricht

**Ethics and Societal Aspects in Early Diagnostics**
Examining social aspects of translational medicine, such as developing diagnostic tools for untreatable diseases, dealing with unexpected findings, assessing quality-of-life, and information disclosure.

“Impressive to learn about how much is needed to successfully implement new medical developments. At the same time, it makes me sad to realize how much we know, but don’t use this knowledge in daily life. Let’s try to change this together!” - D. Bloemkolk, Policy Advisor, Dutch Cardiovascular Patient Organization (Hart en Vaatgroep)

**Entrepreneurship**
Linking entrepreneurial skills and scientific excellence to optimally position new research for subsequent commercialization.

**Medical Technology Assessment**
Assessing the market potential and commercial viability of a product, especially in relation to price, cost and performance.

**Certificate Program in Translational Medicine**
In addition to offering its own training courses, CTMM sponsored some of its most promising PhD students on the Eureka Institute’s Certificate Program in Translational Medicine.

**Course**
**Amount of courses given**
**Number of participants**

<table>
<thead>
<tr>
<th>Course</th>
<th>1</th>
<th>Over 225 delegates from industry, academia and leading research institutions</th>
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<tbody>
<tr>
<td>Intellectual Property Course</td>
<td>8</td>
<td>82</td>
</tr>
<tr>
<td>Translational Research Simulation Course</td>
<td>1</td>
<td>Over 100 researchers</td>
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<tr>
<td>Intellectual Property Course</td>
<td>8</td>
<td>82</td>
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<tr>
<td>Intellectual Property Course</td>
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<tr>
<td>My Own Business Course</td>
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<td>8 participants</td>
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<tr>
<td>MATCH course for Medical Technology Assessment</td>
<td>1</td>
<td>24</td>
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<tr>
<td>Ethical and Societal Issues in the Development of Medical Products Course</td>
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**Ethics and Societal Aspects in Early Diagnostics**

- Daphne Bloemkolk, Policy Advisor, Dutch Cardiovascular Patient Organization (Hart en Vaatgroep)
Impressive Statistics

People, PhD theses, papers, patents, products – take any of those and the number achieved in the CTMM program is impressive. In addition to generating a community of highly educated life-sciences researchers – people with the ability to think ‘outside-the-box’ and change the way things are normally done in order to benefit patients – CTMM has stimulated the creation of numerous entrepreneurial spin-offs and products that will contribute to the future prosperity of the Netherlands.

Diligent Control

Over the course of its lifetime, CTMM engaged a total of 77 SMEs, 27 larger companies, 32 academic institutions and 6 charitable foundations in 25 multidisciplinary project consortia, supplying them with the resources and infrastructures needed to collectively translate basic research into better patient care. That success was not only the result of its content-driven program management; it was also down to careful financial control. CTMM put in place IT systems to facilitate project financial reporting, monitored individual budgets, and created contingency funds to cover unexpected eventualities. And most importantly, it set aside specific funding to finance valorization projects that it knew would be needed to push project results ever-closer to patient benefits.
There is never a dull moment in the Dutch life sciences arena. However, with a constant string of new initiatives, a sea of acronyms, and a plethora of interacting stakeholders in the colourful patchwork that is the Dutch life sciences, it’s not difficult for the overarching objective – the ‘helicopter view’ – to be lost in translation.

**Front-running Dutchmen**

The historical perspective and context in which CTMM started are quite simple. The political urge to increase investment in innovations that would have societal impact was recognized. Life sciences, in particular, were seen as important areas in which the Netherlands’ academic community excels. The paradox, however, was that in spite of all this excellent fundamental science, the number of solutions reaching patients and having a real impact was relatively small.

While the Netherlands Genomic Initiative (NGI) was created to stimulate academic collaboration, three new Technological Top Institutes (TTIs) – the Top Institute Pharma (TI Pharma), Center for Translational Molecular Medicine (CTMM), and BioMedical Materials (BMM) program – were created to stimulate public-private partnerships (PPP) that would accelerate the translation of excellent academic research into real-world healthcare applications. The establishment of these TTIs was unique – something that has not been tried before in the Netherlands or anywhere else in Europe.

The challenge for the TTIs was overcoming the “valley of death” – the gap between academic research and its commercialization – in order to move basic science towards sustainable healthcare solutions that make a difference. TI Pharma would do it for drug development, CTMM for improved diagnosis and molecular diagnostics, and BMM for regenerative medicine and tissue engineering. With the largest government departments involved – the Ministries of Economic affairs, Education and Sciences, and Healthcare – the Netherlands became a real frontrunner in PPP initiatives.

**Connecting with Europe**

Although the TTI solution was unique to the Netherlands, Europe was not unaware of the need to overcome the gap between basic science and the implementation of new insights in healthcare. New public-private initiatives, such as the Innovative Medicine Initiative (IMI) have since been established, creating a huge opportunity for the Dutch life sciences community to capitalize on the expertise and experience built up within the TTIs. As a result, TI Pharma succeeded in creating the European Lead Factory, a pan-European consortium with several Dutch partners including Pivot Park Screening Centre in Oss with its state-of-the-art high-throughput compound screening facilities.

The European Commission has created a number of other transnational research infrastructure initiatives in specific areas, such as biobanking (BBMRI), translational research (SATNIS), imaging (Euro-BioImaging), bioinformatics (ELIXIR) and clinical trials (ECRIN). CTMM became the Dutch scientific representative for EATRIS, which resulted in the EATRIS headquarters being located in Amsterdam.

The only downside is that all these initiatives inevitably involved national branches, all of which have to compete for limited national funding.

**The Dutch ‘Top Sector’ policy on medical technology is a sham**

With the three TTIs barely up and running, the Dutch government introduced its new ‘Top Sector’ policy, clearly not to consolidate what worked well, but to divert national gas reserve (FES) funds away from innovation towards deficit reduction. In other words, the government raised the ante to an unprecedented level by changing course before the ship had even left the harbour. New instruments called Top Consortia for Knowledge and Innovation (TKIs) were introduced to stimulate public-private collaborations, but despite of some successful implementations, not too many researchers are really aware of these instruments or how they work.

On the positive side, the sector got its deserved recognition by the creation of the Top Sector Focus area, such as biobanking (BBMRI), translational research (SATNIS), imaging (Euro-BioImaging), bioinformatics (ELIXIR) and clinical trials (ECRIN). CTMM became the Dutch scientific representative for EATRIS, which resulted in the EATRIS headquarters being located in Amsterdam.

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Lessons learned
A key innovation emerged during the round table discussion was that CTMM had stimulated collaboration between different stakeholders, which opened the way for early diagnoses in many different disease areas. Early diagnoses saves money. Once people have complaints, the associated healthcare costs become far higher. In addition, the annual cost of the sickness benefits becomes far higher. The annual cost of healthcare today can result in revenue losses or at least increased costs for the healthcare environment. In addition, several CTMM networks working on cardiovascular disease, and the affairs of these networks came from business associations. Also that leadership does not necessarily have to come from academia or from industry, but can be shared in an integrated way by the major players, and that the goals of stakeholders involved at an early stage in projects should be extended to include patients and insurance companies. It was also recommended that innovations in early stages should be further supported in order to advance the full potential of disease management. Two additional recommendations based on the success of the CTMM model were that all future models for public-private partnership translational research should incorporate content-driven management structures such as those in CTMM, rather than the purely administrative management structures put in place to previous initiatives, and that they should incorporate an instrument that facilitates technology transfer so that basic science can be transformed into concrete products and applications.

Lugtage: Pioneering Medicine. Together
All projects in the three Top Institute translational research programs have either ended or are about to end. They have resulted in a large number of product or product prototypes that are being pursued in new initiatives, and unique infrastructures such as TRAF that will continue to facilitate translational research well into the future. Without exception, professional content-driven program management has been, and will be, an absolute necessity. Now is the time to decide whether it wants to grasp that opportunity.

CTMM's legacy
The good news is that although the Dutch government Top Sector policy was largely 'window dressing'. Not only one interest: the success of a partnership to deliver outcomes-driven research at an early phase in order to develop MTA models that assist in assessing systems. Within this ecosystem, CTMM's legacy will continue tearing down silos and rewarding partnerships. As a next step, the Netherlands Federation of UniLife and Health~Holland, BBMRI-NL, DTL, EATRIS-NL, Lugtage, and other stakeholders are already creating a blueprint for a proposed new research infrastructure called HEALTH-RI, the Netherlands Personalised Medicine & Health Research Institute. It resulted, by creating an awareness of the need for good data stewardship – making data FAIR (Findable, Accessible, Interoperable and Reusable). The CTMM approach is now serving as a model for other stakeholders. The NGI initiative was successful in bringing many experts, including those in CTMM, rather than the purely administrative management structures put in place to previous initiatives, and that they should incorporate an instrument that facilitates technology transfer so that basic science can be transformed into concrete products and applications.

Front-running again?
Where does this leave us for the future? What have we collectively learned and where are we heading? The NGI initiative was successful in bringing many experts, including those in CTMM, rather than the purely administrative management structures put in place to previous initiatives, and that they should incorporate an instrument that facilitates technology transfer so that basic science can be transformed into concrete products and applications.

CTMM has been successful in taking pole-position in some large Horizon2020 programs. However, this does not necessarily have to come from academia or from industry, but can be shared in an integrated way by the major players, and that the goals of stakeholders involved at an early stage in projects should be extended to include patients and insurance companies. It was also recommended that innovations in early stages should be further supported in order to advance the full potential of disease management. Two additional recommendations based on the success of the CTMM model were that all future models for public-private partnership translational research should incorporate content-driven management structures such as those in CTMM, rather than the purely administrative management structures put in place to previous initiatives, and that they should incorporate an instrument that facilitates technology transfer so that basic science can be transformed into concrete products and applications.
Supervisory Board
The CTMM Supervisory Board is responsible for supervising and counseling the Executive Board in its decision making. A complete list of Supervisory Board members is provided to the right.

Executive Board
The CTMM Executive Board is responsible for the strategic research program and related operational processes. Management of the CTMM program includes preparation of calls and evaluation of proposals for funding, monitoring of the program and scientific quality check, and the acquisition of new partners and funding. The Executive Board also organizes meetings of the Supervisory Board, International Scientific Advisory Committee and General Assembly. The CTMM Executive Board comprises Peter Luijten, Chief Scientific Officer, and Heidi Hamers-Hajduk, Managing Director.

International Scientific Advisory Committee (ISAC)
The International Scientific Advisory Committee gives advice on submitted projects and conducts the mid-term review of CTMM projects (May 2011 for First Call, June 2012 for Second Call and January 2013 for Joint Call projects). It assesses the balance and overall quality in the project portfolio and performs an independent check on how well CTMM is meeting its strategic objectives laid out in the business plan. The ISAC is composed of international experts in their respective medical fields.

General Assembly
The General Assembly comprises representatives of all partners in CTMM projects, including supporting foundations. The Meeting of the General Assembly takes place annually.

International Scientific Advisory Committee (ISAC)

Supervisory Board

CHAIR

General Assembly

Executive Board

Supervisory Board

Until December 13, 2014
J.F. Sistermans, Ph.D. (Chairman)
H. van den Berg, MA
H. van Houten, Ph.D.
Prof. F. Kuipers, Ph.D.
J.H.J. Mengelers, Ir.
G.J.H.C.M. Peeters, MA
Prof. H.M. Pinedo, M.D., Ph.D.
Prof. H.A.P. Pols, Ph.D.
L.N. Sierkstra, Ph.D.
H.E. Viëtor, Ph.D.
M.G. Wubbolts, Ph.D.

Since December 14, 2014
J.F. Sistermans, Ph.D. (Chairman)
Prof. J.A.M. Raaijmakers, PhD. (Vice-chairman)
Prof. F. Kuipers, PhD.
H.E. Viëtor, PhD.
Prof. A.M. Kruisbeek, PhD.
F.M.C. Leemhuis, PhD.

International Scientific Advisory Committee

Prof. R.S. Reneman, Ph.D. (Chairman)
Prof. J.A. Andersson, M.D., Ph.D.
J.P. Armand, M.D., MSc (until January 31, 2013)
R.S.B. Balaban, Ph.D.
J.B. Bassingthwaighte, Ph.D.
R.G. Blasberg, M.D.
Prof. L. Degos
H. Hermjakob, Ph.D.
W.J. Jagust, Ph.D.
Prof. D.J. Kerr
Prof. U.D.A. Landegren, M.D., Ph.D.
R.I. Pettigrew, M.D., Ph.D.
A. Tedgui, Ph.D.
Prof. T.P. Young

Northeast 2014

CHAIR

General Assembly

Executive Board

Supervisory Board

CTMM staff, from left to right:
Eric Caldenhoven, Program Manager; Peter Luijten, Chief Scientific Officer; Peter Verhagen, Assistant Controller; Erna Erdtsieck-Ernste, Program Manager; Heidi Hamers-Hajduk, Managing Director; Jan-Willem Boiten, Project Manager TraIT; Henny Bruinewoud, Program Manager; Marjoke Kortas, Communications Manager; Odette Veron, Office Manager; Petra Bongers, Administrator; Bert Gerritsma, Controller; J.F. Sistermans, Ph.D. (Chairman)
Pointing to the future
CTMM and TI Pharma join forces within Lygature.