

Nanomedicine in The Netherlands: social and economic challenges

Background Note for First and Second Chamber MPs visiting
the High Tech Campus Eindhoven (April 16, 2010)

2010, May 31

**Bart Walhout, Ira van Keulen and Rinie van Est (Rathenau Instituut),
Ineke Malsch (Malsch Techno Valuation)**

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Colofon

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Rathenau Instituut
Anna van Saksenlaan 51
P.O. Box 95366
2509 CJ The Hague
The Netherlands
Telephone: +31 70 342 15 42
Telefax: +31 70 363 34 88
E-mail: info@rathenau.nl
Website: www.rathenau.nl
Publisher: Rathenau Instituut

Translation: David Bennet, Technical University of Delft
Layout: Rathenau Instituut
Graphic: Max Beinema Graphic Design

Preferred citation:

Walhout, B. Van Keulen, I. Van Est, Q. and Malsch, I. Nanomedicine in The Netherlands: social and economic challenges. The Hague, Rathenau Instituut, 2010

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1 Introduction

Nanotechnology promises employment, sustainability and health. The Dutch government invests heavily in it. But how do we achieve these promises? In preparation for a parliamentary debate about nanotechnology on 21 April 2010, the Rathenau Institute initiated a working visit of MPs to one of the most promising areas of its application: healthcare. This note sets out the promises, challenges and issues surrounding 'nanomedicine'.

Why nano?

Bacteria, viruses, unhealthy diet or lifestyle, and errors in the genetic code, They all make us sick in different ways. But they also have one thing in common: they all operate at the molecular level. Nanotechnology manipulates and analyses matter at this level and therefore promises groundbreaking insights and solutions. Nanomedicine fits into a long tradition of medical science to search for biological mechanisms of disease at deepening physiological levels. According to researchers and developers, this knowledge shall lead to earlier detection, more accurate treatment of diseases and new treatments such as artificial organs.

Nanotechnology also offers possibilities for the miniaturisation of various medical devices and their integration with (wireless) ICT. Diagnosis and treatment can take place outside the laboratory or clinic, even at the patient's home. Continuous monitoring of health seems to be within reach, also for healthy people.¹ In short, nanotechnology promises a wave of new research areas in medicine and new applications for healthcare.

A long-term task

The ambitions for nanomedicine are high. "A revolution in the prevention, diagnosis and treatment of many chronically debilitating diseases", Dutch nano-scientists claimed in 2007. No small task - the researchers anticipate twenty years development time. Even with the good starting position for nanomedicine in The Netherlands – a strong electronics sector and high quality life science research – it will be a long term task to fulfil its promises.

At the end of 2009, the government continued its financial support of research and development through the proposed High Tech Systems & Materials (HTS&M) initiative of the Economic Structure Enhancing Fund (FES). This funding is used for research for understanding the causes of the emergence of diseases and translation into functional nanomaterials, nano-electronic devices and artificial molecular machines. But the clinical

¹ In general, this category of applications is referred to as 'medical nanotechnologies'. But in actual practice research in nanomedicine and the development of medical nanotechnologies go hand-in-hand. Therefore in this paper we mainly use the term 'nanomedicine' or we speak about medical applications of nanotechnology.

value of these new applications needs to be demonstrated. Bottlenecks are discussed in this note.

Once developed, nanomedical applications can also present big challenges. Consider the commitment to prevention made by molecular imaging which has stimulated the growing exchange of detailed health information and increased opportunities for self-management patient care. We therefore look at the trends and their implications for the patient in this note as well.

Orientation Towards the Future

Nanotechnology promises to give key support to future health care such as the comprehensive ideal of "PPP Medicine": predictive, preventive and personalised. Timely and tailored intervention improves quality of care and life. A fourth element is often added as well: participatory. Care should be organised around the patient's medical specifics rather than around institutions. Moreover, the patient's active participation is expected to be pursued.

This kind of future visions is full of technological promises which often will not be fulfilled. But visions give direction and change our view of future developments - in this case of care and health. The pressing question then is whether technological change fits into healthcare challenges. Healthcare is suffering from high costs, looming labour shortages and complex information exchange. What solutions does nanotechnology provide for these social issues? And what do nano applications do to ensure quality, access and affordability of care? What is expected of patients and do they need support?

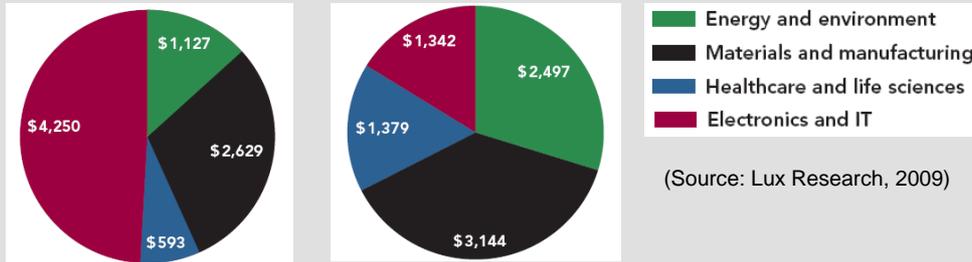
This note sets out a number of important points for MPs to prepare for the visit in April 2010. What exactly are the promises of nanomedicine (page 7)? What researchers and companies in The Netherlands are engaged in nanomedicine (page 12)? How can we fulfil the promises (page 15)? And finally, what are the main political issues for this field of application (page 21)?

Market statistics and investment in nanomedicine

Compared with other nanotechnology application areas there seem to be fewer nanomedicine products on the market. Precise figures are difficult to determine because a nano-scale drug or device is not always mentioned explicitly. Nevertheless, the European "Nanomed Round Table" project tried and came up with 45 commercial products and two diagnostic products in 2008 including nanoparticles. The same project identified 60 products in development phase. It does however warn that the figure is not very reliable because no company could be involved in the investigation.

It is not strange that there are not many products on the nanomedicine market. Medical products always have long market introduction times because clinical trials

are needed. Many, such as (complex) drug delivery systems, are still in clinical trial phase (see also page 16).



(Source: Lux Research, 2009)

Graphic 1: Private investment in nanotechnology in 2008 by sector at Fx (in \$US millions)

Graphic 2: Public investment in nanotechnology in 2008 by sector at Fx (in \$US millions)

The predictions for market potential are promising. The figures mainly relate to drug delivery and less to diagnostic and reconstructive applications of nanomedicine. The Lux Research report "Nanotechnology Advances Regenerative Medicine" (2007) shows that some reconstructive applications, above all dental treatments, are already on the market. Other applications are still in the developmental stage or in the clinical trial phase. The Lux report does not specify market forecasts for nano-based regenerative products. However the British consulting firm, Científica, with the well-known nanotechnologist, Tim Harper, does so for nano-based drug delivery systems (DDS). According to this organisation, the DDS market was \$US3.39 billion in 2007 and is predicted to rise in 2012 to \$US 26 billion and \$US220 billion in 2015.

Another report from Lux Research 2009 shows that so far private investment in nanomedicine seems to lag behind public investment. There is therefore still a major challenge (see p12). In 2008, the global private investment in nanotechnology for healthcare was \$US593 million (i.e. 7% of total business investment in nanotechnologies) and public investment \$US1379 million (i.e. 16% of total public investment in nanotechnologies).

2 Promises of Nanomedicine

Nanomedicine covers a wide range of nanotechnology research and healthcare applications. Nanomedicine tries to utilise the growth of knowledge and engineering capabilities at the nanoscale to apply such knowledge and technology in clinical care: for diagnosis and treatment in the medical environment but also elsewhere for monitoring the health of chronically ill patients or of healthy people.

Diagnosis

In the field of diagnosis of diseases and disorders nanomedicine promises to propel the move to earlier diagnosis and decentralisation of care.

Early Diagnosis

Where genetics looks for genetic predictors of disease, molecular nanomedicine looks especially for indicators of possible diseases (Boenink, 2009). Such detectors are called “biomarkers”. These include changes at the molecular biochemical level (e.g. DNA, RNA or proteins). Biomarkers can also be modifications in genes such as methylated DNA. Instead of medicine specialities such as epidemiology which looks for external pathogens (viruses or bacteria) or pathological anatomy which looks for morphological changes in tissues, nanomedicine looks for the very first signs of an illness without the person actually already having signs of sickness. The idea is that by this means earlier and more accurate diagnoses could be made, which would save lives and work cost effectively.

Nanomedicine offers two routes for early diagnosis:

- In vitro tests for specifying molecules associated with a specific disease (biomarkers) using biosensors;
- In vivo measurement of specific molecules associated with a specific disease (biomarkers) using imaging techniques with nanoparticles as contrast agents.

An example of an in vitro test is one which the U.S. NanoSphere company developed. This involves specific biosensors which can measure blood levels, for example, of protein enzymes which are produced by dead heart muscle tissue and indicate that a patient has had a heart attack. Previously, these low blood levels were very difficult to measure and doctors frequently sent patients home wrongly. Now gold nano-particles with a special coating composed of DNA or antibody fragments with the protein enzymes are attached in the same coating to a biosensor chip. A digital camera can then read the protein value. The patient only needs to undergo a blood test and a antibody test. Heart disease can be detected earlier with such a test and it can also to be detected within a few minutes. So it is possible to investigate whether someone has just had a heart attack.

Philips initially developed the same kind of tests. For example, the company is well advanced in developing the lab-on-a-chip platform: MagnoTech. MagnoTech is based on the application of magnetic nanoparticles which can be manipulated by an external

magnetic field. MagnoTech can measure many markers quickly at once. It is a compact platform made from recycled plastic at low cost and can be manufactured in large quantities. The platform provides quantitative measures of relevant cardiac enzymes from a drop of blood within five minutes without expert intervention. It is intended to use the test in the hospital as well as for point-of-care applications. Recently Philips also developed another point-of-care in-vitro test for drug use - cannabis, heroin, cocaine, benzodiazepines, amphetamines, etc. can be quickly identified with a saliva sample. The application was called a *roadside drug test* and compared with an alcohol breath test. The major advantage of these tests is the clear result obtained on the spot (point-of-care) so rapid (medical) decisions can be taken.

Another method of molecular imaging is early diagnosis by using nanoparticles as contrast agents which bind to specific biomarkers these biomarkers can be made visible in the body. Traditional imaging methods mainly focus on differences in water content or density in the body in order to detect abnormalities. Molecular imaging with MRI, SPECT, PET and other techniques provides a much better resolution and sensitivity. Biological processes in living organisms can be visualised at the cellular level. Small tumours to which magnetic contrast agents such as iron oxide nanoparticles specifically attached to carriers, for example, can be visualised by MRI and this is already approved by the FDA. Neurological as well as cancer and cardiovascular diseases can be diagnosed early in the future. Specific radioactive contrast media with much higher sensitivity may be used with SPECT or PET imaging in scanning the patient.

Decentralised diagnosis

One of the biggest successes in the field of nanotechnology is the diagnostic lab-on-a-chip: a laboratory with the size of a stamp with microscopic channels to conduct chemical and physical analysis of a drop of blood. Such analysis can also be done in vitro with a hand-held diagnostic device that gives a result within a few minutes. Examples are the MediMate developed in Twente and the MagnoTech platforms developed by Philips researchers. The MediMate can measure the lithium content in blood. Manic-depressive patients are prescribed lithium to combat mood swings but because the wrong dose can have serious consequences, the lithium levels need to be monitored regularly. Until now this required a hospital or outpatient visit involving long waiting times. With Medimate the patient might be able to test him or herself at home (see also page 20).

Lab-on-a-chip technology has many applications (though not all are on the market). There are chips developed to measure the influence of drugs on cancer cells. Other chips may be used to determine sodium, potassium, calcium and magnesium concentrations which would be useful for kidney patients to measure the sodium content in their urine when they are at home. Nowadays, there are chips on the market to identify fever caused by a lack of calcium and phosphorus in cows milk at an early stage. These tiny laboratories give the patient greater freedom of movement. He or she can use the tests at home - or on holiday – and the tests will give the results within minutes. Treatment costs can decline. The lithium chip, for example is made of glass (unlike silicon chips) and costs at around fifteen Euros each. The MagnoTech chip is made of plastic with even lower production costs and suitable for mass production.

Treatment

Nanomedicine also creates new opportunities for medical treatment. This involves increasing the efficiency of pharmaceutical treatment by targeted drug delivery and less invasive therapies. There is also reconstructive nanomedicine which seeks both tissue re-growth (regenerative medicine) and to restore bodily functions (think of an artificial retina).

Efficient therapy with fewer side effects

In the absence of new active substances, the pharmaceutical industry's hopes are based on improved drug delivery. Using nanotechnology, it is possible to package the active ingredients so that they are not distributed generally in the body but only released at the desired location. This increases the efficiency of the drug. At the same time side effects caused by the widespread distribution of drugs throughout the body are reduced.

There are two types of drug delivery. The first generation is a passive method. The drug is in hollow structures such as liposomes and injected into the body. Liposomes (filled spheres but also other nano-constructs) penetrate with difficulty through healthy tissue, but much more easily through diseased tissue in such as tumours. Due to their rapid growth the blood vessels in tumours more often 'leak' and tumour cells are less dense than healthy cells. This is called the enhanced permeability and retention effect of the affected tissue. Nano-spheres can also be made to make the drug go to the right place by an external signal, released, for example by a change in the acidity of the tissue or tumours by ultrasound or a strong light pulse.

The second generation uses the active method. Nanocapsules with molecular antennae as directional molecules enclose the drug. If they come into contact with certain structures, the antenna molecules specifically recognise molecular characteristics of the disease source, bind to it, and give up their content locally. Such nanoparticles can be constructed that containerise the drug Taxol, which is cancer consuming, attached to a vitamin such as folic acid. These second generation drug delivery systems sometimes also use imaging techniques to carry the drug to the right place. Examples include metallic nanoparticles attached to a drug such as Prednisone and subsequently fired by an external magnetic field.

With a serious illness such as cancer, swallowing several drugs can sometimes be counterproductive for the patient. A new application of nanotechnology in development is the multifunctional platform that contains active nano substances in various modules and stores them at the right time and place to do their work later.

Less invasive therapies with fewer side effects

Nanotechnology can also fight cancer effectively through thermo-therapy. Small nanoparticles accumulating in the blood vessels of tumours are swept with light, sound or magnetic waves. The particles heat up and the heated tumour tissue dies. Side effects are rare and thermo-therapy appears to be an effective alternative to chemotherapy or surgery.

The right therapy at the right time

Besides the indiscriminate spread of drugs in the body, there is another difficult problem for pharmaceutical investigation, namely that the response for a given patient to a therapy is difficult to predict specifically. Currently dosage for each patient is the same. However, it would be preferable to tune the therapy to individual patients or to at least differentiate between groups of patients. This is called personalised healthcare. This should lead to more effective treatment, fewer side effects, increased patient compliance (because you as a user notice the difference) and the promise – when timely applied - of the extension of the period of healthy life. Molecular imaging may help in personalisation of care. This approach allows the predetermination of the response of women with breast cancer to hormone therapy. It can also be used for the optimisation of the pre-clinical and clinical phases of new drugs.

Recovery and regeneration of body cells, tissues, organs and functions

Opinions differ about whether regenerative medicine fall under nanomedicine – the European Technology Platform think so, the European Science Foundation (ESF) not. ESF includes it under nanobiomaterials or new materials but not under nanomedicine applications. It depends on contributions from the involvement nanotechnology without nanotechnology necessarily having to be central. Anyway, nanotechnology provides a major boost to the field of regenerative medicine (tissue engineering and stem cell research).

It does this in two ways. First is the regeneration of tissue with nanoscale structured biomaterials. These include nano-fibers, peptides and other nanomaterials that provide a matrix within which cells can grow and tissue can be formed. This also includes specific nanobiomaterial bioactive molecules (ie proteins and peptides) that encourage contained cell growth and the stimulation of tissue repair by signalling molecules. This is useful with implants when a nano-coating ensures better adhesion because it stimulates the growth of surrounding tissue.

In addition, there are cell-based therapies. This is the treatment or prevention of diseases by insertion of cells first adapted outside the body. Nanomaterials can be used, for example, to promote the self-healing properties of cells. Research shows that adult stem cells in carbon nanotubes can stimulate the neurons in the brains of rats to change. In addition to the repair of body tissue, nanotechnology can also help to restore body functions by building artificial organs. A well recognised example is the development of the artificial retina.

Monitoring

The new diagnostic and treatment capabilities or nanomedicine will affect medical practice in the clinic and also have impact beyond. Medical procedures are increasingly carried out outside the hospital, clinic or practice location. This is also referred to as decentralization of medical care. Nanotechnology plays a crucial role in this trend of decentralization by contributing to the miniaturisation of technology and the development of smart environments. In the future patients want the possible opportunities both to manage their own illnesses and for continuous health monitoring. These offer many advantages. They

allow the patient as an employee or parent, for example, to continue to participate in society more easily.

Self-monitoring Your Health

An example has already been discussed on page 8: the lab-on-a-chip. The Medimate can enable bipolar patients to monitor their lithium levels themselves. In the same laboratory in Twente they are working on the development of a mini-laboratory for men to test the quality of their sperm at home.

As a next step, already underway - the introduction of so-called “wet sensors” (with biocompatible coatings) in the body or the brains of patients (in vivo). At present it is already possible to check your pulse and measure temperature and blood glucose by a chip placed under the skin. The information is then transmitted wirelessly to an IT unit. An example is the Philips IntelliCap platform - in fact, a tiny electronic pill equipped with sensors that can be read outside the body which at the same time checks the drugs on board that are to be delivered.

Continuous Monitoring of Your Health

Nanotechnology increases the means for wireless body monitoring involving the development of ever smaller and more efficient computer chips and battery technology. By designing the internal structure of nanoscale batteries, researchers may have substantially higher returns. The ideal is however to extract energy from the environment. Nanoscientists are developing energy scavengers which from a mix of light, movement and temperature variation can extract enough energy for a sensor to operate and transmit the data wirelessly.

With small chips, cheap sensors and new energy technologies, nanotechnology makes a ‘smart environment’ possible. As part of their programme HUMAN++ the Belgian IMEC, participating in the Dutch Holst Centre, is developing a body area network (BAN), a network of sensors and actuators that is carried in your body, monitors many health parameters and can communicate with the outside world via WiFi or other mobile network. The network offers certain services to the user such as the management of a chronic illness or monitoring sports and fitness performance. IMEC already developed a device for heart and brain activity measurement with wireless ECG and EC, respectively.

3 Sketch of the Dutch nanomedicine landscape

In The Netherlands all kinds of institutions carry out relevant research in molecular and cellular biology and biophysics; nanofluidics, physics and (bio)chemistry or functional nanoparticles, pharmaceuticals and cell biology. The Dutch research community in the field of nanomedicine is organised in a number of research programmes.

In the new FES High Tech Systems and Materials Program (2011-2014) nanomedicine is one of the four application areas. This research builds on previous research in FES programmes including NanoNed and Biomade. The main lines of research in the FES field of nanomedicine are:

- Unravelling the causes and development of diseases
- Nanotechnology for diagnostics
- Molecular imaging
- Nanotechnology for targeted drug delivery
- Nanotechnology for reconstructive medicine.

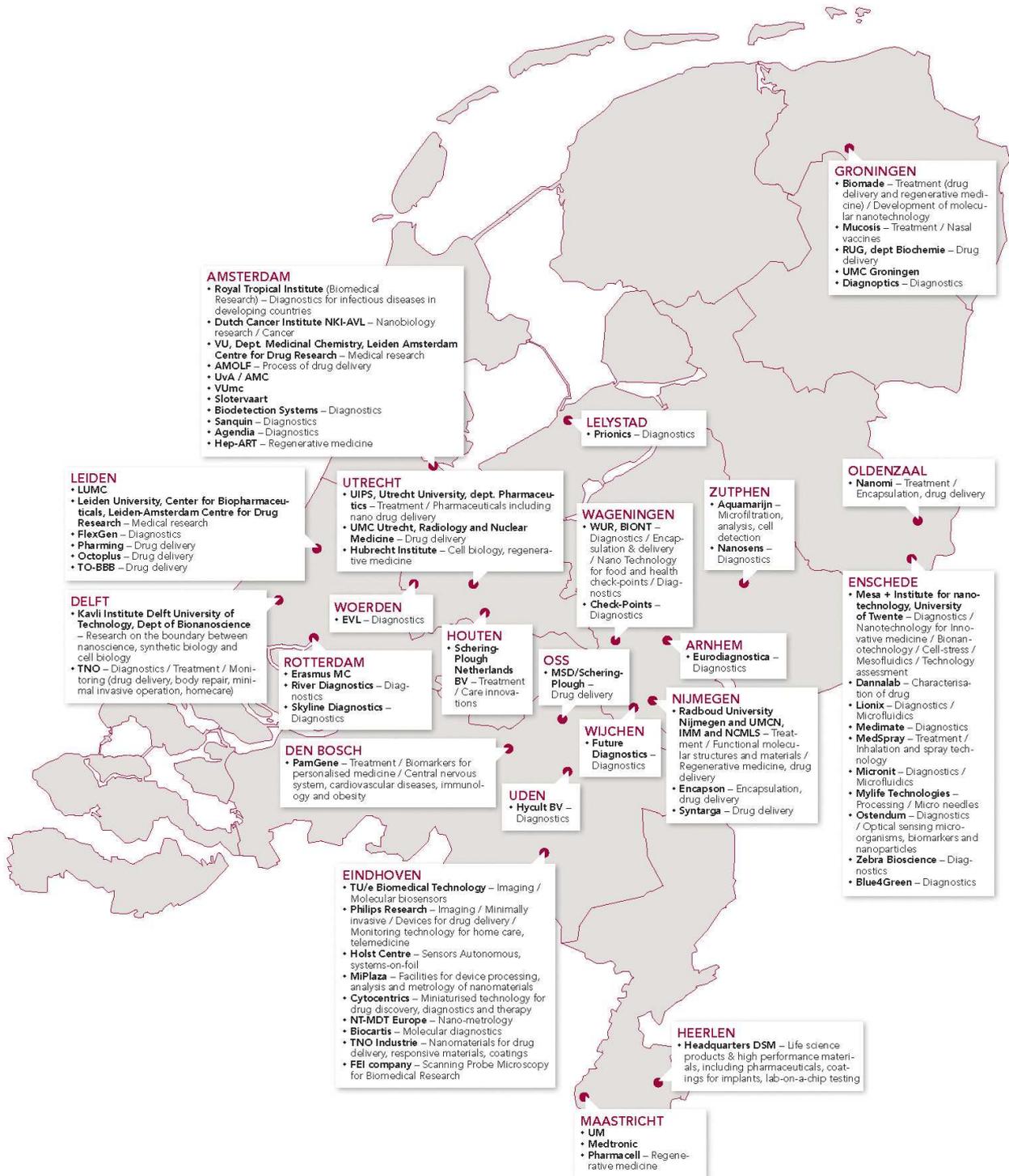
In addition, a dedicated research agenda has been established with three current programmes which include nanomedical research: CTMM (Center for Translational Molecular Medicine), BMM (Biomedical Materials) and TI Pharma, (see table). These three programmes work together and most recently in February 2010 announced a joint investment of €28 million in seven projects.

Of the Dutch players in nanomedicine, Philips is especially strong in European research networks. The European Technology Platform (ETP) Nanomedicine is led by Philips and Siemens. Other members of the ETP are the Dutch organisations RIVM, University of Twente, VUMC, and a mirror group coordinated by The Netherlands Agency NL (formerly SENTER-NOVEM). Participants are Philips Healthcare Research, UT/MESA+, Wageningen UR, VUmc, UvA, Syntarga, Nanomi, Progentix and Aquamarine. The implementation of the strategic research agenda of the Nanomedicine ETP (nano-pharmaceuticals, diagnostics and regenerative medicine) is funded by the European Commission Seventh Framework Programme for RTD and the ERA-NET EuroNanoMed. This ERA-NET is a cooperative of national research funders and the European Commission. The Dutch partner is Agentschap NL.

| Network | Applications | Research | Budget | Public funds |
|---|---|--|--|--|
| NanoNed (2004-2010) and HTS&M (2011-2014) | Diagnosis and treatment. NanoNed: bionanosystems, chemistry and physics of single molecules, nanofluidics. HTS&M: Nanomedicine, nano & society | Basic and Applied Research | NanoNed total: €235 million. HTS&M total: € 300 million. | NanoNed: FES total €120 million. Universities €88 million. HTS&M: FES total: €125 million. |
| CTMM and TU/e (2007 – 2012). Research agenda is implemented in 18 projects. There are 105 partners, including all Dutch University Medical Centres, various universities and 83 companies (including Philips, MSD, Dutch Heart Foundation, the Alzheimer's Foundation, the Diabetes Fund and the Dutch government). | Personalised medicine with molecular diagnostics, imaging and theranostics - systems that are both diagnosis and treatment - cancer, cardiovascular disease, neurodegenerative diseases and infectious diseases and immunity. | Product development | CTMM total €400 million. 2007, 2008 and 2009 €265 million Joint call with BMM, TI Pharma 2010: €28 million for seven projects, or which have 3 CTMM funding, €200 million | Dutch government, public knowledge institutions and businesses €85 million €80 million. The rest must come from new partners (business plan CTMM). |
| BMM (2006 – 2011) There are 11 projects. Partners are several Dutch companies, all Dutch UMCs, several universities, the Heart Foundation and The Kidney Foundation. | Diagnosis and treatment: new biomedical materials and applications. Diseases: heart disease, muscular, renal disease. | Product development (pre-competitive). | BMM total €90 million. | Dutch government €45 million. |
| Top Institute Pharma TI. Founded in 2006. Duration: 4 years. Commission Veerman recently called for follow-up. Comprises 49 consortia with 28 companies 45 companies | Drug Formulation, termination and targeting, including nano-based products. | Product development. | In 2008 to €43,660,181, - (from Annual Report 2008). | Min VWS grant €21,551,690, -. Academic partners: €10,371,670, -. |
| STW | Funding applied research, including nano-medical research | Application oriented research | €19 million in STW Perspective and €10 million through open call | 25% industry contribution For projects over €500,000, - |

Table 1: Networks

Map of the Dutch nanomedicine landscape



4 How to fulfil the promise?

Nanotechnology offers opportunities to organise our healthcare differently: more effectively, personalised and partly outside the hospital. The benefits are a better quality of care and of life. But the fulfilment of these promises is dependent on a number of conditions: affordability, shorter development times and patient support in dealing with new responsibilities.

Quality, equal access and affordability are key concepts in discussions about care. It is not clear that nanotechnology will make only a positive contribution there. In 2006, the Health Council overviewed social issues: safety, equity, protection of privacy, diagnosis, changing relationships between doctors and patients, and human enhancement. These are familiar questions but with new challenges through the application of nanotechnology, says the Health Council. And prior to the societal challenges there are challenges in research and development: good cooperation between science and industry, and an appropriate regulatory framework.

Nanomedicine thus faces many challenges. Here we consider a number of challenges in treatment, diagnostics and monitoring. First we look at questions about innovation in developing new treatments. We look at questions about early diagnosis. Monitoring and privacy issues are changing relationships between doctor and patient focus. We illustrate each of these challenges with a case. In separate boxes, we pay attention to safety issues and equitable distribution on a global level. On page 21 we take stock of the political discussion about what nanotechnology can do for the future of care.

Employing the knowledge about nanoparticles

The possibility of risks of synthetic nanoparticles are the main theme in the public debate on nanotechnology. In contrast with 'accidental' exposure to nanoparticles in paints and other products the exposure to nanoparticles in using nano-drugs is just part of the intended effect of the medication. Although relatively much is known about potential risks or nanotechnology in medical applications, there are still gaps in knowledge. Greater knowledge is needed about biocompatibility and toxicity, how nanoparticles in the body may possibly spread and accumulate, and whether the current test methods are adequate.

There are already strict guidelines for drugs and medical devices. Particular attention is therefore paid to the specific risks, which nanomaterials may comprise in the authorisation files. The availability of alternatives and the clinical benefits of the products are included. Knowledge about nanomaterials in the medical field is already quite thorough. Therefore the advice of the RIVM is to use this knowledge actively for other application areas. One point of concern for the regulations is the products at the interface between drugs and medical devices (see page 16).

Nanotechnology for everyone?

Like most countries in the world The Netherlands has signed up to the UN Millennium Development Goals. By 2015 poverty in the world has to be reduced substantially and improving health is a major objective. According to the European Group on Ethics, it is a moral obligation that the application of nanotechnology contribute to them, but this is not easy. The Health Council concluded in 2006 that scientific and technical progress in healthcare investment requires locations where resources are

available. Without deliberate effort to implement these, developing countries will therefore not benefit from applications of nanotechnology or will be late in doing so.

Nanotechnology seems to offer plenty of opportunities for cheap diagnostics. For example, the Royal Tropical Institute (KIT) together with NanoNed develops applications for the detection of tuberculosis. By now laboratory research is needed for this detection. Chip manufacturer NXP is able to produce a highly sensitive nanosensor that makes the time-consuming cultivation of bacteria unnecessary. Part of the work is basic research and yet it depends on many factors including whether the nano-sensor is available on the market. According to Prof. Paul Klatser of KIT, companies are concerned about logistic problems and the protection of patents, problems which also apply to other technologies.

Two efforts are important for developing countries to benefit from nanotechnology. First is the ability of researchers from developing countries to collaborate with colleagues in rich countries. This could be through the European Commission 7th Framework Programme, but researchers have difficulty in finding each other. The European Commission promotes international research cooperation through the ICPC-NanoNet project. The Netherlands also provides funds, but the Health Council wonders whether they are sufficient. Second, the Nanomed Round Table recommends that European organisations such as UNESCO are involved in the development of nanomedicine. Much research is now directed to diseases of affluence while poverty-related diseases such as tuberculosis remain neglected. The European Commission's Nanobio-RAISE project argued that, as with all major public investment, the discussion on priorities needs to be pursued in the context of global health, which can be critical towards the further reduction of mortality in western societies.

Treatment: bridging long development times

High-level knowledge, promising research, but few products on the market. The development of nano-drugs seems to be suffering from the infamous innovation paradox. Yet it rather is an 'innovation dilemma': drug manufacturers lack discoveries of new medicinal substances and are waiting for new technologies to make existing drugs more effective to administer and with fewer side effects. But as long as the clinical relevance of nano-applications has not yet been demonstrated, the pharmaceutical industry is not convinced of the potential (see box on MediTrans, page 17). Moreover, a net cost-saving effect can be achieved by reducing side effects (patients can go home earlier), but that advantage may only be made use of when cooperating with insurers and government, which in turn needs a more mature product.

Waiting Games

In the NanoNed Technology Assessment (TA) program such an innovation dilemma is called a waiting game. Various workshops suggest this situation also applies in nanotechnology for food or polymer electronics. The European Commission is trying to resolve the situation for healthcare applications with the establishment of the Nanomedicine European Technology Platform, a large public-private consortium with large multinational industrial players such as Philips and Siemens in the lead. But despite this new business model the platform has not found productive symbiosis. Developing new drugs is expensive. This makes the fate of new inventions uncertain.

'Drug' or 'device'?

Drug development normally takes a long time. New drugs must first go through extensive clinical trials before they can be put on the market. Many of the (complex) nano drug delivery systems are still in the phase of clinical trials. A search of the American clinicaltrial.gov database provides 77 hits on

nanoparticles, of which 67 are related to cancer. The keyword “liposome” delivers 425 hits, 330 of which are related to cancer. But the approval process can be shorter. According to the European Group on Ethics, it is necessary to first determine whether the drug is a new medicine or just a new drug delivery system. “Nanomedical products may combine different mechanisms of action, be they mechanical, chemical, pharmacological or immunological for clinical instance. The mechanism of action is a key factor in deciding whether a product should be regulated as medicinal product or as a medical device.” Assessment pathways for medical devices are considerably shorter and would be obvious for applications where the effect of the active component is known.

MediTrans: from opportunity to clinical practise

The development of effective, safe and innovative drug delivery systems is a complex process. Over the last decades, new techniques based on nanoparticles have progressed, but the pace of discovery by the large pharmaceutical companies and hence to reach the market is still too low. The European Commission has funded, inter alia, MediTrans to take research in targeted drug delivery using nanoparticles one step nearer to the market.

MediTrans works with thirteen companies, eleven universities and six specialised research centres from different European countries. The project is coordinated by the University of Utrecht. Other partners are the Dutch FOM Institute AMOLF, Merck, Philips Research and Eindhoven University of Technology. Together, the participating partners represent a good cross section of the European nanomedical field.

According to MediTrans coordinator, Gert Storm, the initiative is working well, but it stops too soon to lead to real success. At present, four nano-applications from the project are being reviewed by the industry. This is hopeful but for a major industry player to actually pull the project over the line, clinical proof of principle must be provided. A small patient study can be decisive in giving industry the stimulus for developing and producing large patient studies: the costly and time-consuming clinical trials. Storm hopes that with a few proven applications, industry becomes more committed to nanomedicine.

Storm draws two lessons from the project: establishing public private partnerships such as MediTrans at the European level and TI Pharma, BMM, CTMM and the HTS&M programme at Dutch level is a good strategy. But public-private partnerships have also been accompanied by much oversight and general requirements. This provides for openness and transparency but is also time consuming and puts the assessment of content under strain. A development time of about five years can easily need one and a half year's prior preparation. It is therefore important that the Dutch research programme has sufficient support. The second lesson is the importance of a helping hand for spinoffs. In The Netherlands SenterNovem, for instance, could provide such programmes.

Diagnosis: earlier detection is not always better

"Cancer found too early" was the headline of an article in the science section of NRC Handelsblad on November 28, 2009 describing the problems involved in the diagnosis of prostate cancer. Three quarters of all people initially diagnosed develop prostate cancer each year in The Netherlands, about 2400 people with this disease. Enough reason to screen every man, so it seems. But in the majority of cases, prostate cancer does no harm. The problem is that there are no good tests that distinguish with sufficient precision between an active or a dormant tumour in the prostate with the result that increased screening also leads to more interventions with all their nasty side effects.

The test for aggressive prostate cancer is by analysing pieces of tissue: a biopsy. But a quarter of all tumours are missed by biopsy. Research on biomarkers (see page 7) may improve the diagnostic tests. In 2007, the PCA3 test, a prostate cancer test that can detect specific RNA molecules in urine, was put on the market. The PCA3 test has been developed at Radboud University Nijmegen and is now used increasingly as an indicator to perform semi-biopsy. CTMM is also working on research on diagnostic tests with improved predictive value.

Health as a source of continuing concern

The specific use of the PCA3 test shows the current limitations in molecular diagnostics. Biomarkers may be a better or cheaper alternative to laboratory diagnostics in existing clinical diagnosis (the diagnosis that the doctor carries out). However, the search for biomarkers is also motivated by the trend of increasing prediction and prevention (see box on biomarkers for Alzheimer's). Applications of nanotechnology will reinforce this trend, such as in molecular diagnostics. Relatively inexpensive diagnostic techniques that have little stress for the patient and immediate results take away technical and economic objections to the extension of screening and prevention. Against the background of earlier promises of genetic research and a growing (bio)medical awareness among citizens, this effect however calls for reflection.

Any form of diagnosis brings uncertainties. But in molecular diagnostics, these uncertainties are linked to individual performance and behaviour. Currently medical diagnosis for patients is related to what is seen as healthy for everyone. The focus on individual biochemical profiling and monitoring brings with it new responsibilities: health and disease are more an individual thing, with weighty choices to take into account. Undesirable medicalisation lies in wait in this development. The latest analysis of trends in biotechnology for the Dutch parliament is that the predictive value of information about the origin of diseases continues to be difficult to interpret. This makes great demands on the exchange of information between doctor and patient. Adequate patient knowledge and good embedding into healthcare procedures are important conditions.

Biomarkers for Alzheimer

Alzheimer's disease is a common and dreaded form of dementia. Diagnosing Alzheimer's disease is difficult. The most obvious symptom, accumulation of abnormal proteins in the brain, can be measured only after death. In the living patient, we now use a combination of neuro-psychological tests, blood tests and physical examination, and sometimes MRI scans and EEGs. The results are interpreted by a multidisciplinary team until a diagnosis is achieved. In molecular medicine therefore there is a diligent search for suitable biomarkers. CTMM, for example, is working on a combination of imaging techniques (PET and MRI axial scans) and biochemical analysis of spinal fluid.

The expected usefulness of biomarkers is threefold. They could serve as a tool for early diagnosis, perhaps just before the first symptoms of Alzheimer's occur. In addition, the hope is that they provide clues for developing new therapies which take advantage of the proteins in question. And finally, the adoption of biomarker tests which can be examined quickly and easily, whether and by whom new drugs will really catch on. This would considerably shorten the development time of new drugs. Yet research on biomarkers for Alzheimer's disease also involves ethical dilemmas and in the NWO program Responsible Innovation an entire project is devoted to this case.

For example, there is still no effective therapy available for Alzheimer's disease. This raises the question of how desirable early diagnosis is. Do you want to know that you have early stage Alzheimer's when there is little that can be done? This question is made more difficult by the high

requirements that biomarkers have for measurement. The biomarker needs to be clearly linked to the molecular processes that cause Alzheimer's, which are manifested early in the disease process and are visible in laboratory tests. Moreover, the biological processes that underlie the disease are unusually complex and the chances are that most biomarkers appear to be indicators of the disease 'only' indicating an increased risk. This makes it difficult to determine whether or not biomarker tests produce useful information.

This uncertainty also induces other questions. The medical developments are heavily focused on the natural history of the disease, while environmental factors might be neglected. The extent to which Alzheimer's is experienced as stressful depends mostly on the ability of the patient to manage the symptoms in their own environment. Wouldn't carers' attention not be more important? And is Alzheimer's not just a nightmare for many people because their autonomy is extraordinarily valued? How tolerant are we with people lacking abilities? For introduction to the healthcare market these questions will need to be answered as well.

Monitoring: self-care is not automatic

The successful development of lab-on-a-chip technology and other biosensors using nanotechnology is crucial for the development of point-of-care technologies: medical devices which can be deployed by physician or patient on site. This development, sometimes called 'pocket pathology', reinforces the trend to decentralisation: the organisation of health care beyond the walls of the hospital. The hope in this is for cost savings and being closer to the wishes and needs of the individual patient. 'For example, Philips and Achmea, a health insurer, are working together in the "Care Within Reach" programme for solutions for three major chronic diseases in The Netherlands: cardiovascular disease, diabetes and COPD.

Computerised monitoring and control of behaviour

A future with the 'doctor in your pocket' does not automatically work in favour of the patient. Consider the development of easily portable sensors with which heart rate and brain activity of cardiac patients can be continuously measured. Early detection of cardiac arrhythmias gives better protection and reduces the costs of rehabilitation. The sensors connected to a PDA (personal digital assistants, many mobile already provide such functionality), which can be connected to an emergency service. However, the collected data from the sensors may also be examined for general patterns, which give insight into the relationship between health and behaviour. Especially when sensors are placed in the body, because many chronic conditions give better results by continuous monitoring than repeated snapshots, it is conceivable that detailed information on the relationship between health and social behaviour becomes an important battle. The exchange of detailed health information must therefore be made under clear conditions.

Changing roles and responsibilities

Medical equipment in the home entails new roles and responsibilities. The shift from patient to health consumer already tests the skills of both doctor and patient. But recent research into the use of heart rate monitors (ECG) by Professor Nelly Oudshoorn, Twente, shows that the patient's role goes far beyond that of health consumer in the use of medical equipment. The patient him or herself is partly responsible for the diagnosis. For such diseases as diabetes this is already standard practice, but this is well organised with guidance from websites and patient organisations.

Examination by the Rathenau Institute of medical devices for home use shows the general need for coaching in many cases. Dave Blank, chairman of the Dutch Nanotechnology Initiative, sees for example that in the introduction of MediMate multi-reader (see box on MediMate) pharmacists play an important role. In a special issue of the Pharmaceutical Weekly he predicts that other tests using the same principle will soon follow after the lithium test. Diagnostics will be moving from the hospital or general

practice to the living room. "As a result, support and information by the pharmacy will be more important than they are now," says Blank. "Furthermore, you may wonder who is responsible for the patient's responses to the test. Is it the manufacturer who developed the test or the pharmacy which gave the explanation?"

MediMate: a typical spin-off

In The Netherlands the MediMate multi-reader is perhaps one of the most used examples in lectures on the applications of nanotechnology. The multi-reader allows a number of laboratory tests for blood values to be performed as easily as for insulin by diabetes meters. The first example on the market is expected to be the personal a lab-on-a-chip meter for lithium of bipolar patients. The patient does not have to wait for referral to the psychiatrist's medical laboratory or hospital and then wait for the results. The MediMate multi-reader symbolises important changes in healthcare. Inexpensive and handy diagnostic equipment will allow many analyses to be performed by patients themselves.

The history of MediMate is exemplar as well. A combination of high quality PhDs, an entrepreneurial professor - Spinoza prize winner, Albert van den Berg – and funding to develop an initial business plan and links with a regional hospital made up an innovative ecosystem. As a spin-off of the MESA+ research centre at University of Twente site, Medimate can also attract graduate master students. Already this has led to a spinoff of the spinoff: a MediMate lab-on-a-chip sensor for the determination of milk fever in cows.

The actual launch of the multi-reader will show how applications such as MediMate will have an impact on healthcare systems in the sort term. A workshop as part of the Nanotechnology Public Dialogue on nanotechnology showed that the multi-reader's promise that patients can themselves perform measurements is a step too far for bipolar patients, psychiatrists and health insurers. That the measurement may be performed in the psychiatrist's practice is still a significant improvement compared with the laboratory.

5 Political issues

Innovation is important for the future of healthcare. Nanotechnology promises solutions to key challenges. But the fulfilment of those promises requires more rapid development times and new roles for the patient. Various challenges have been reviewed in the previous pages. In addition we list a number of opinions from the field below.

Healthcare in The Netherlands is challenged by the growth of chronic diseases, shortage of medical personnel and increasingly high public demands. Preventative and targeted intervention is an opportunity. Nanomedicine may contribute to this by acquiring knowledge of the history, diagnosis and treatment of diseases at the molecular level. The European NanoMed Round Table project showed that this promise is widely supported by science, policy, industry and also patients. Still, Ethicists in the project asked who benefits and economists asked when such promises can be realised. Promises alone do not make innovation. Additional important conditions are:

1. More certainty about market opportunities

The Netherlands has a strong position in nanomedicine and our government is investing heavily in public-private programmes such as TI Pharma and BMM CTMM (see page 12). To start investment from the pharmaceutical industry the European Technology Platform supports a more important role for industry when research proposals are reviewed by public funders. Another way to foster innovation is by unlocking information about markets and disease. In order to assess market opportunities, health economists need information from doctors. The Nanomed Round Table stressed the importance of interaction between stakeholders to encourage increased knowledge about developments in nanomedicine among physicians.

Should government projects open up creation of information about diseases and markets?

2. Proper regulation of innovation

Industry calls for pre-market and post-market surveillance of innovations in medical technology to be accelerated. According to companies, the strict regulations for medical devices do not reflect current innovation practice. Another problem is financial reimbursement. The Council for Health and Care (CVZ) concluded in 2005 that the system for combined diagnostic and treatment (DBC) is too rigid for rapid deployment of proven improvements through innovation. Problems in the reimbursement structure were recently underlined by the Healthcare Innovation Board (ZIP). At the end of 2009 the Committee for Health Insurance recommended on this point to enter into a system of conditional funding for innovations in healthcare. The issues in regulation and reimbursement were raised for applications of nanotechnology, but apply generally to healthcare innovations as well.

Do new developments in nanomedicine pose specific challenges for regulation and reimbursement or is there a general problem?

3. Protection of responsibilities for patient

Patients are expected to play a more active role in healthcare delivery. This is not always easy. The predictive value of early diagnosis is expected to remain difficult to quantify. In a special issue on nanotechnology of the Pharmaceutical Weekly, Roderik Kraaijenhagen, cardiologist and medical director

of the NIPED (a research institute specialising in prevention and early diagnosis), claims that "self-management and empowerment of the individuality is very necessary for development of healthcare." But according to Kraaijenhagen, stimulating self management cannot be enough. "A new technology must fit into accepted healthcare practise. Otherwise, there is no follow-up and the patient is the victim."

Are responsibilities of the patient clear enough and who is responsible for protecting them?

4. Balance between prevention and control of behaviour

Applications of nanotechnology make possible new medical technologies in the home. Health monitoring in the home can save costs and enable faster responses. But the information provided by (continuous) monitoring will also provide insight into relationships between health and behaviour. From a preventive point of view, it is logical to use this information in negotiating with the patient. A greater freedom of movement for the patient is thus also accompanied by new opportunities to interfere.

How should the right balance be reached between empowerment and coercion or pressure from a health perspective?

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Who was Rathenau?

The Rathenau Instituut is named after Professor G.W. Rathenau (1911-1989, who was successively professor of experimental physics at the University of Amsterdam, director of the Philips Physics Laboratory in Eindhoven, and a member of the Scientific Advisory Council on Government Policy. He achieved national fame as chairman of the commission formed in 1978 to investigate the societal implications of micro-electronics. One of the commission's recommendations was that there should be ongoing and systematic monitoring of the societal significance of all technological advances. Rathenau's activities led to the foundation of the Netherlands Organization for Technology Assessment (NOTA) in 1986. On 2 June 1994, this organization was renamed 'the Rathenau Instituut'.