Amazing

Leading in innovation for health and care

2015/2016
Dear reader,

Let us introduce ourselves.

Erasmus University Medical Center Rotterdam is committed to a healthy population and excellence in healthcare through research and education (www.erasmusmc.nl). It excels in various research fields, studying fundamental and clinical domains as well as public health and prevention. Research at Erasmus MC is at the heart of society, resulting in innovation, quality improvement and more effectiveness in patient care. Erasmus MC is in the top ten of best medical institutes in Europe (QS World University Ranking 2014). It participated in 165 FP7 projects of the European Commission and it hosts 20 ERC grantees.

Everyday, more than 10,000 dedicated employees are contributing to our results in cure, care, research and education.

The overall research aim of Erasmus MC is to translate bench discoveries to bedside applications. Its annual research budget amounts to €139.7 million. Innovative companies are set up based on our scientific results and existing companies start new developments based on our discoveries. The impact of Erasmus MC on the Dutch economy is substantial: in 2012, it contributed €3.8 billion gross value added (GVA) to the Dutch economy and it indirectly supported 40,556 jobs. Bibliometric indicators place Erasmus MC in the top 20 of clinical medicine worldwide; its publications are cited 1.75 times the world average.

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In addition to scientific research, patient care and education are core tasks of Erasmus MC. It is the top referral center for a region of about five million inhabitants. The complete spectrum of medicine is offered, from disease to health and from individual to public healthcare. Erasmus MC is also the largest medical school in the Netherlands, with ~3,100 medical students and 234 PhD graduations in 2013. It offers BSc, MSc and PhD programs to train the next generation of medical practitioners and researchers. Together, the students and employees at Erasmus MC improve the individual patient care and public health of tomorrow.

This magazine gives you an impression of the diversity and quality of research, cure, care and education of Erasmus MC.

We hope you enjoy the read!

The editors
Our mission:

Introduction

Professor Ernst Kuipers
Chairman of the Erasmus MC Executive Board

“As large and versatile university medical center (UMC) we especially focus on acute care, on complex care that makes great demands on specialist knowledge, on innovation of care and prevention. Those tasks are directly linked to research in which fundamental, translational and clinical research are represented.”

“We are building at our current location. There will be a new hospital here in 2017 that is ready for the future: aimed at the patient, flexible and durable. It is not the medical disciplines that determine the layout of the new construction, but themes formed around patient groups, like the elderly, children and oncological patients and around diseases, such as cardiovascular diseases and infectious diseases.”

“The world is changing and so are we. Technological possibilities are constantly increasing, but the budgets are becoming more limited. We have to make choices. We will invest our efforts and money in focus areas. Together with other UMC’s we are working on a division of labor. This makes collaboration even more important. Medical Delta (with Leiden University Medical Center and Delft University of Technology, ed.) is a good example.”
Erasmus MC is committed to a healthy population and excellence in healthcare through research and education.

Professor Jaap Verweij  
Dean and Vice-Chairman of the Erasmus MC Executive Board

"Erasmus MC is connected to the world. We already take part in international and European projects and consortiums extensively and we are stepping this up. One example is EIT Health, the European Knowledge and Innovation Community, in which Erasmus MC participates with a large number of knowledge institutes and parties from the corporate world in fourteen European countries. Through this interaction we share our knowledge and increase the power of the research."

"Education is also becoming more international. The masters studies and PhD tracks of Erasmus MC attract talented people from all over the world. We encourage our students of medicine to gain experience abroad during their basic training. Encountering other cultures and habits within health care is very educational and fits our international position."

"In the end research and education serve health care. By combining our research in institutes within the organization of Erasmus MC, we make it clear: this is our expertise. Those institutes in turn consist of Centers of Excellence, hubs in which the best people from various disciplines combine forces. A good example is the Academic Breast Cancer Center Erasmus MC - Havenziekenhuis (Harbour Hospital). This is part of Erasmus MC Cancer Institute, in which departments such as Surgery, Internal Oncology, Plastic Surgery, Radiotherapy and Pathology work together with Havenziekenhuis Rotterdam."

"We see it as our job to bring knowledge and scientific findings to society. Knowledge valorization is essential to realizing our mission. And any economic gain is used to stimulate new research. Erasmus MC Technology Transfer Office is essential to realizing that ambition."
Continuous improvement
It is Erasmus MC’s ambition to continuously improve the quality of its care. Promoting patient participation by offering access to medical records is one of our frontrunner initiatives. Recently Erasmus MC has become a strategic partner of the International Consortium for Health Outcomes Measurement (ICHOM).

An ambitious new build project is scheduled to be finished in 2017. Each patient will have a private room with direct daylight and a bathroom in the new medical center. This will enable Erasmus MC to offer the best possible care.
Erasmus MC research

- Number of PhD graduations: 227 (2014)

- Total research budget: EUR 139.7 M (2013)
  - University-allotted budget (1st budget source): EUR 44.9 M (32%)
  - External subsidies, excluding subsidy amount intended for external partners (2nd, 3rd and 4th budget source combined): EUR 94.8 M (68%)

- Some prestigious personal grants obtained by Erasmus MC researchers in 2013-2015

  Veni: Jan Hontelez, Debby van Riel, Gustavo Higuera, Maarten Titulaer, Ana Bobinac, Klazina Kooiman, Roberto Narcisi, Zhenyu Gao, Ferry Cornelissen

  Vidi: Vincent Jaddoe, Fernando Rivadeneira, Dimitris Rizopoulos, Jurgen Marteijn, Sander Herfst

  Vici: Caroline Klaver

  ERC Starting Grant: Tokameh Mahmoudi

  ERC Consolidator Grant: Caroline Klaver, Vincent Jaddoe

  ERC Advanced Grant: John Foekens, Reuven Agami, Wim Vermeulen, Elaine Dzierzak

  ERC Proof of Concept: Chris de Zeeuw, Jan Hoeijmakers

Erasmus MC research: The European top

Erasmus MC performs internationally outstanding research. It is in the top ten of best medical institutes in Europe according to the Times Higher Education ranking 2013. Erasmus MC excels in many fields, studying fundamental, clinical and epidemiological domains as well as policy-related ones. Erasmus MC’s top position attracts the best researchers worldwide as well as talented students.

Collaboration

In modern medical research, collaboration among research groups is crucial. Erasmus MC strongly encourages its researchers to work together with scientists from other institutes in the Netherlands and abroad.

A national example is ‘Medical Delta’, in which Erasmus MC collaborates with Leiden University Medical Center and Delft University of Technology. Medical Delta aims to force breakthroughs in medical technology through collaboration. On an international scale, Erasmus MC researchers participate in numerous large consortia. An example is the FP7 funding program of the European Commission, which closed in 2013. Erasmus MC has been very successful in the FP7 program, with a total of 165 project participations, 50 of which were coordinated by Erasmus MC. The first projects within Horizon2020, the runner up program of FP7, have already been granted to Erasmus MC researchers.
Erasmus MC citation scores period 2009-2012/13

- Number of peer-reviewed articles (including original research articles, letters, notes and reviews) published in journals processed for the Web of Science version of Thomson Science Citation: 10,663
- Total number of citations excluding self-citations: 137,549
- Mean normalized citation score (MNCS): 1.85
- Mean normalized journal score (MNJS): 1.54
- MNCS/MNJS: 1.20

1 MNCS: This is the overall field normalized impact indicator of the international citation position of a research unit. An MNCS above 1.0 means that the output of the research unit is cited more frequently than the ‘average’ publication in the subfield(s) in which the research unit is active.

2 MNJS: This is the overall field normalized impact indicator of the international journal position of a research unit. An MNJS above 1.0 means that the citation score of the journal set in which the research unit has published exceeds the citation score of all papers published in the subfield(s) to which the journals belong. In this case, one can conclude that the research unit publishes in journals with a relatively high impact.

3 MNCS/MNJS: This indicator matches the impact of papers closely to the publication pattern of research units. If the ratio MNCS/MNJS is above 1.0, the impact of a research unit’s papers exceeds the impact of all articles published in the journals in which the particular research unit has published its papers (the research unit’s journal set).

Read more about research at Erasmus MC:
www.erasmusmc.nl/research/?lang=en

Introduction

Find out more about European research projects coordinated by Erasmus MC on:

HorizonHealth.eu
in touch with European research
Erasmus MC Graduate School

Erasmus MC Graduate School is an umbrella organization for five internationally renowned, KNAW accredited, research schools. These offer ambitious young people a solid basis for a career in medical and life sciences. Five officially accredited Research Master programs and five PhD programs are organized by the research schools. These programs present students with the challenge and opportunity to become medical researchers who can make a contribution to the future advancement of medical science.

Erasmus MC offers the following educational programs:

Program (Number of students)
- Medicine (2,500)
- Nanobiology (140)
- Clinical Technology (90)
- Research Masters (150)
- PhD programs (1,000)
- 28 Medical specialization programs

Read more about education at Erasmus MC:
www.erasmusmc.nl/onderwijs/?lang=en
“Many scholars want to go to Harvard or Stanford,” says professor Steven Lamberts, General Director of International Affairs at Erasmus MC. “But we offer the same quality.”

Since 1983 the American media organization U.S. News & World Report has been ranking the quality of clinical research by the best medical universities in the world. For the first time Erasmus MC has reached the top 20. "A great confirmation of our status," says Lamberts. "Of the twenty best medical universities in the world, thirteen are in the United States, four are in England, one is in Canada, one in Sweden and one in the Netherlands. Erasmus MC is a global contender. We can be proud of that. If you look at how the U.S. News & World Report ranking has been compiled, you can see that we excel in the quality of our scientific publications. Based on that criterion we are in the top ten institutes in the world.”

Ideal partners
“The term 'internationalization' often brings to mind the exchange of students, but there is not much point in directly stimulating that,” Lamberts feels. “Our challenge mainly lies in the development of a policy of internationalization that is 'output-driven'. By that I mean: we want to aim at top level research together with international partners.”

Lamberts feels the ideal partners are institutes from countries that are experiencing a strong economic growth: “Various universities in China, India, Thailand, Indonesia and Brazil. Those are the rising stars, the winners of the coming decades. There are a lot of talented young people there and they also have the means to finance research at the highest levels.”
Overall score | no. publications | Global reputation | Total citations | no. highly cited papers
--- | --- | --- | --- | ---
1 Harvard University | 100 | 1 | 1 | 1
2 Johns Hopkins University | 81.2 | 3 | 2 | 2
3 University of California - San Francisco | 74.4 | 6 | 7 | 5
4 University of Oxford | 72.4 | 27 | 3 | 13
5 Duke University | 70.9 | 13 | 15 | 7
6 University of Toronto | 70.9 | 2 | 9 | 3
7 University of California - Los Angeles | 69.4 | 11 | 5 | 12
8 University of Washington | 69.2 | 12 | 13 | 9
9 University of Pennsylvania | 68.5 | 5 | 12 | 6
10 Mayo Clinic | 67.8 | 4 | 39 | 4
11 Stanford University | 67.7 | 17 | 6 | 17
12 Columbia University | 66.2 | 21 | 18 | 15
13 University of Michigan | 66.0 | 9 | 14 | 10
14 Imperial College London | 65.4 | 19 | 16 | 16
15 University College London | 64.7 | 8 | 17 | 8
16 University of Pittsburgh | 64.3 | 10 | 19 | 11
17 University of Cambridge | 63.6 | 80 | 4 | 43
18 Karolinska Institute | 62.6 | 14 | 10 | 18
19 Erasmus MC / Erasmus University Rotterdam | 61.0 | 20 | 37 | 14
20 University of California - San Diego | 60.9 | 45 | 29 | 33

Global University ranking for Clinical Medicine according to U.S. News & World Report (www.usnews.com)
With head and heart

Thijs Spigt, Director of the Technology Transfer Office (TTO) of Erasmus MC, warns against too much openness: “On a global scale we all miss out on many billions.”

Open
Spigt: “Many scientists are very willing to share their knowledge. But if you share too much, the chances are your discoveries can no longer be protected, for instance by patents.”
But surely as researcher you can’t keep everything to yourself?
“Of course, you can share some information at a convention, but do this without blowing your own chances,” Spigt says. “If you have a loaf of bread, you can just show the middle, but leave out the crust. Everyone understands you are showing them a loaf of bread, but there are certain parts you keep to yourself for the time being.”

Ignorant
Keeping knowledge to yourself is something many researchers find difficult and Spigt can understand this – “What the heart thinks, the mouth speaks” - but he also sees the economic opportunities. He owes this insight to studying Biology in Amsterdam and Business Management at the Erasmus University in Rotterdam, and to his years of experience working for pharmaceutical companies. Spigt: “My heart lies with Biology, my head lies with Business Management.”
The opportunities to make their discoveries economically useful that scientists miss out on, represent a value which the Director of TTO says runs to the billions worldwide. Not only do scientists with university centres make these mistakes, it also happens within large pharmaceutical companies. “Completely unnecessary!” says Spigt. “The realisation that discoveries in medical biology also have an economic interest, is something many scientists do not think about enough. This is due to different reasons: the pressure to publicize, ignorance, indifference. It’s not exactly that they’re not willing, it’s more that they are unaware of the possibilities, the do’s and don’ts. The reasoning is: if I can just publish my findings quickly, the new medicine will be produced, and I don’t really need to establish a company for that. Well, that is a big mistake. Only by protecting scientific discoveries and developing them corporately, can they truly be made available to society.”

Intellectual property
TTO is crucial for increasing this awareness. Spigt: “What we say, is: guys, be careful! Before you send something off to a magazine, or before you present something to a convention... come and see us. One conversation can be enough and it is not complicated or scary. We are here to help you. We can advise you on how to handle your intellectual property, which doesn’t always have to lead to filing a patent application or establishing a company. It can also be a matter of claiming copyright or a trademark which provides enough protection.”
The visible results of the TTO include the number of patents granted and the number of companies established. Spigt calls these the results at the back of the TTO process. However he finds the activities at the front equally important. Spigt: “You have to know what is happening in the scientific world. Where do we stand? How unique is this finding? Can we protect this discovery with a patent? And that insight can gain you a lot in the long run.”
TTO will focus on promoting valorization, secure ownership of inventions, and the dissemination of new findings into society.

Either, existing companies start new developments based on our discoveries, or innovative companies are set up based on Erasmus MC research results, which may benefit from our Incubator facilities. In 2014, Erasmus MC Holding BV contained 31 companies. Two new companies were supported in their start-up in 2014.

Our Incubator is located in the Rotterdam Science Tower and houses three companies. These companies employ more than 40 people. With that, the maximum capacity of the Incubator has been reached and an extension of the capacity is foreseen.

Erasmus MC owns 113 patent families and we signed 8 license agreements in 2014. The Legal department evaluated 720 agreements, a plus of almost 15% over the previous year.

More detailed information: www.erasmusmc.nl/tto
‘Research aimed at individual treatment of the patient’
“In tailored therapy the focus must lie on the tumor and on the patient,” says professor Ron Mathijssen of Erasmus MC Cancer Institute. “It is the knowledge of both that will make the therapy more effective.”

The professor of Individualized Oncological Pharmacotherapy emphasizes: “We can increase the effectiveness of the current medicines by taking the personal factors of the oncology patient into account. For instance by choosing the correct time to take medication and considering lifestyle factors.”

In personal medicine, or tailored therapy, there are two aspects. Mathijssen: “On the one hand: which tumor characteristics are there and which medication is best suited to those? On the other hand: how, how much and when do you give this medicine and how much of it actually reaches the tumor? The second aspect is determined by the body of the patient itself. The best therapy is found by studying both aspects.”

**Therapeutic window**
How much medicine do I give? This is one of the questions Mathijssen focusses on. “If you do not give the patient enough anti-cancer medication, it does not work effectively enough. If you give too much, it often causes serious side effects. You have to stay within these boundaries, the ‘therapeutic window.’”

The correct dose is currently determined based on research among a group of patients. This leads to one registered dose. “This is odd, because there are enormous differences between patients,” says Mathijssen: “If you treat everyone with the same standard dose, then it is certain that this dose will be too high or too low for a number of patients. The optimal dose for an individual is influenced by numerous factors. Consider hereditary factors and physical characteristics such as gender, age, height and weight. But also how the organs are functioning. Does the patient also suffer from other diseases and is he taking medication or alternative medicines for these? Someone’s lifestyle (diet, smoking, alcohol) and the time of day the medicine is taken also influence the eventual concentration of the medicine in the blood.”

The goal is therapeutic drug monitoring. Mathijssen: “In the end we want to measure the concentration of the medicine in the blood of each patient and adjust the dosage accordingly. This is already common in people receiving donor organs, but for cancer patients this is only just starting to receive attention.”
Cola
The way a drug is taken also influences the concentration in the blood and thus the effectiveness of the medicine. A medication that is soluble in fat will not be absorbed as well on an empty stomach as in combination with a portion of fries. Mathijssen is now studying the taking of an anti-cancer drug with... a can of cola.

“It concerns Erlotinib, which is prescribed to patients with lung cancer. Erlotinib is not absorbed well if the stomach is not acidic enough. Hence the combination with cola, a fairly acidic drink. Every patient partaking in the study will receive one course of medication with and one without cola. This will show which works best.”

Many cancer patients take other medicines besides their anti-cancer drugs. Over forty percent of these experience unwanted interactions between these medicines and the anti-cancer drug. Mathijssen: “A good registration of medication is very important. It allows the oncologist to oversee the patient’s medicine use.”

Unfavorable time
The time of day medication is taken can also influence the concentration in the blood. How the body deals with the absorption and breaking down of medicines is strictly regulated by the biological clock. Mathijssen: “I’m studying this together with professor Bert van der Horst of the Genetics Department. He is mainly interested in the biological clock from a genetics viewpoint, my interest lies in the metabolism of the patient.”

He explains: “The special proteins which break down medication in the liver (enzymes) might work far more powerfully at night than during the day, when a person is moving, working and eating. It is imaginable that the liver works faster and better at night. A pill taken in the evening will therefore be broken down faster than a pill taken in the morning.”

Recent studies on Sunitinib and Tamoxifen, which are used for renal cell cancer and breast cancer respectively, showed that the time of day the drug is taken influences the concentration of the medicine in the blood. Mathijssen: “If a patient always takes his medicine at an unfavorable time, the concentration in the blood will fall lower than if he were to take it at a more favorable moment. An incorrectly chosen moment in combination with a dose that is too low for that particular patient, could lead to a concentration which is not effective enough against the cancer. So for certain medications it is vital to determine the best moment to take them for each patient.”
Looking at art is an excellent way to train image analysis and pattern and emotion recognition, is the viewpoint of Erasmus MC. It is also a great method to practice passing on information. These are important parts of performing a diagnostic procedure.

Medical students visit the halls of Museum Boijmans Van Beuningen in Rotterdam in small groups. There they situate themselves by a work of art. In one of the tests one student looks at the artwork, while the others sit with their backs to it. By looking at it and describing it, the first student passes information on to the rest of the group. These students form an image which they can clarify by asking the correct questions.
Erasmus MC ran a pilot in the college year 2013-2014, but the intention is to make “looking at art” a fixed part of the curriculum of Medicine.

Examples of experiences in the first year:
“Students realize that describing what you see is harder than it seems.”
“When you have seen an abstract painting, you assume that the second painting will also be abstract. I have learned not to develop tunnel vision and to keep an open mind as much as possible.”
“You have to be able to make it clear to a colleague what it is you have seen exactly, so that another doctor can form a clear and accurate picture of what is wrong with the patient.”
A healthy life begins before pregnancy
Plan of attack against infant death

The chances of a healthy baby are not equal for everyone. Lifestyle, but also the social circumstances of the parents - such as poverty - play an important part. This was shown by a study at Erasmus MC and led to a prevention program that caught on.

When Eric Steegers came to work in Rotterdam in 2001, the gynecologist and researcher noticed that the rate of infant death around the time of birth was abnormally high. In some neighborhoods in town it was up to four times as high as the national average. A risky lifestyle and bad social circumstances were the most important causes, research commissioned by Steegers showed. He says: “We also saw differences between native Dutch people and non-natives, but the largest problem was the social circumstances, like income and housing.”

With this data professor Steegers turned to the local authorities and got approval for a Rotterdam plan of attack against infant death. By now this successful approach is making its way into other cities under the motto: Healthy Pregnancy 4 all. This is partly thanks to the support of the Ministry of Health, Welfare and Sport.

Early advice
Steegers says that especially the early stages of pregnancy need to get more attention. “The first months of a pregnancy are important to the development of a child. But the first contact between mothers-to-be and their midwife and other health workers does not take place until after this important period. Too late. Women should receive advice about their way of life before the pregnancy even begins. Think of taking folic acid, giving up smoking, not drinking and healthy eating. If all this goes right in the first months, there is a smaller chance of problems during the pregnancy, but also in the later life of a child and adult. A healthy life begins before conception.”

Advisors from target audience
How do you encourage people to improve their lifestyle? Steegers: “That is possible if you focus attention on it in the right way and at the right time. We use advisors from the target audience itself. They can reach future mothers with a kind of ‘tupperware party’. And we make sure general practitioners can easily refer mothers to the right support. We also developed the coaching program Smarter Pregnancy. This gives people tips on healthy living through the internet and their cell phone, through emails and texts.”

Correct aid
The central message of Healthy Pregnancy 4 all is that every mother has the right to the correct aid. This is partly an organizational challenge. Organizations sometime work at cross-purposes.
Steegers: “But in the trial cities we see for example that midwives and gynecologists are making good arrangements for tailored care. The same goes for the local health
authorities, clinics and the Youth and Family Centers. We get everyone around the table. In this way we create care pathways in which we see what a woman needs in a certain situation and how we can organize this as smartly as possible.”

Since research in Rotterdam has shown that it concerns many more matters than just the lifestyle of the mother, in the other cities attention is also focused on the social circumstances of families. Steegers: “We look at poverty, domestic violence, debt repayment and housing. These factors influence the pregnancy. If necessary, we can call in the help of social workers for example.”

Results
Are more healthy babies being born in the trial cities? Steegers: “The research into this has not been completed. But I have complete confidence that the project will be successful in this regard. We do already know that both care workers and parents are satisfied. We see that mothers start living healthier lives; especially when the father also joins in. We will see what the consequences are for matters like birth weight and infant death.”

However, Steegers looks at the work that has been done with satisfaction. “No one still denies that prevention begins with the wish to become pregnant. As Rotterdam’s medical center, Erasmus MC has taken on a leading role in a development which is being copied all over the Netherlands.” The message of Steegers is all about prevention: “The health of the future population is partly dependent on the care for the future pregnant women of today.”
Hair shows stress

A new method enables Erasmus MC to detect the stress hormone cortisol in hair. This allows you to look back months – or with long hair, years – in time.

‘A new world opens up, the findings and new insights are numerous’
A bit of stress is good for a person. If you have to sit an exam for example, stress gives you a better memory beforehand. The body produces extra adrenaline and the stress hormone cortisol. This elevates the heart rate and blood pressure. The body produces extra sugar and that can provide more energy short term. But stress is not only caused by psychological factors.

Dr. Liesbeth van Rossum: “You see exactly the same biological stress reaction in pain or a severe flu. In these cases extra cortisol is also produced and the blood pressure goes up. That is a healthy reaction. Stress only becomes a problem if it lasts too long. For instance because of chronic pain or continuous work pressures.”

**Strong fluctuation**

“You can measure stress by determining the cortisol value in blood, saliva or urine,” Van Rossum continues. “If there is more stress, the cortisol value goes up. The cortisol value fluctuates strongly during the course of the day. It is lowest at night, it peaks just before waking and it gradually declines as the day progresses, with the occasional spike. Giving blood is a stressful moment for many and this influences the measurements.”

The existing methods of measurement only show the values for a particular moment. The great thing about the new hair measurement is that it produces an average score. Van Rossum: “The hair on your head grows by about a centimeter a month. So we take a centimeter of hair and see how high the average cortisol value was in the month that piece of hair was growing.”

**Risky**

We would die without cortisol. It ensures that many processes in the body take place properly. Van Rossum: “But if you have too much of it, or if you’re very sensitive to it, then the cholesterol and the blood pressure go up, fat accumulates especially in the abdominal area and the blood sugar value increases. These are risk factors for – among others – diabetes, cardiovascular disease and obesity. That is why chronic stress, be it psychological or physical, is so risky.”

**Shift work**

The new measuring method developed by Van Rossum and her team has also made new research possible. “A new world opens up. The findings and new insights are numerous,” she relates. Van Rossum was able to show that people who work in shifts have a higher average stress hormone level. “Their sleeping pattern is disturbed, which disturbs the cortisol levels. On average they are more likely to suffer from obesity. It appears that this cannot just be explained by an increased tendency to eat junk food at night. It could just as easily be caused by an excess of cortisol.”

In the same way she was able to show that toddlers who go to school for the first time suffer from a much higher level of stress in that first month than previously. By now Van Rossum is receiving numerous requests from scientists abroad who want to use the new measuring method.

**Obesity**

As resident endocrinologist Van Rossum focusses largely on obesity. She is now using the new stress research to determine how obesity works. A striking result of the study is that from a BMI of 30 up – which is classified as obesity – the average cortisol level increases dramatically. Both in adults and in children.

She says: “Up to a BMI of 30 the cortisol level barely rises, but above 30 it suddenly shoots up. We know a highly elevated cortisol level leads to a higher weight, but it is unclear why it suddenly goes up so sharply in people with obesity.” A logical explanation could be that cortisol does not only produce extra weight, but that the increased weight also influences the extra production or decreased breakdown of cortisol. “It does appear to be a vicious circle,” Van Rossum says. “That is what we are trying to determine.”
SkillsLab is unique in the Netherlands

“Safety squared”

“The safe learning environment we offer here, eventually leads to safer care. Safety squared, we call it.” So says Madelon Panman. She is manager of the SkillsLab at Erasmus MC. On this page follow some impressions.
The SkillsLab is intended for three groups. First of all doctors who are in training for a surgical specialization. They train basic skills there, like the suturing of blood vessels. Secondly doctors from Erasmus MC who excel at a certain element of their field and give a workshop. Finally medical companies who run courses for their (potential) clients, such as doctors and nurses.

**Deftness and anatomy**
Professor of Anatomy Gert-Jan Kleinrensink relates: “Deftness and anatomy are the pillars of surgery. Both elements are present in the SkillsLab, physically and organizationally. The anatomical dissecting room and the rooms where doctors can train their skills, are directly linked here.” Manager Madelon Panman: “But it’s not just about technical skills. You also learn to work together here. For instance, how do you ensure a safe environment where people feel safe enough to bring up issues with each other? An operation assistant has to dare ask a surgeon a question, without being hindered by status.”

The SkillsLab continues to develop more options for team trainings. Panman: “Surgeon, anesthetist and assistants practice together. The added value? Knowledge and insights are more easily shared and it leads to a better collaboration in the clinic.”
Professor Robert Jan Stolker, Department Head of Anesthesiology at Erasmus MC, talks about a high tech simulator. That’s an artificial patient with which anesthetists can practice situations endlessly without harming the patient.

Stolker: “We started working with this type of simulator in 2008. They enable us to train an unlimited number of scenarios. A number of technical moves can be trained, such as the inserting of ventilation tubes. And you can mimic situations that are life-threatening.”

More self-confidence
Anesthetist Christian Grass is program leader of Simulation Education within the SkillsLab. He says: “The most important advantage of simulators is that no patient is burdened and that the course participant does not have to worry about the safety of a living person. If it goes wrong, we simply press the reset button and restart the exercise, until it goes right. This gives the student more self-confidence and knowledge when he faces a real patient.”

Realistic training
“Compare it to puppet theatre. There you also know that it’s not real, but everyone calls out: ‘Look out, behind you!’ Even though it’s only a puppet, you go along with the game.”

Endless errors
“The use of simulators is essential to my field of expertise. The basic course is purely an exercise in manual dexterity. How do you hold the scoop? How do you stand?” So says Arjun Koch. The doctorate research of the gastroenterologist focused on the role of simulator trainings in the training to become an endoscopist.

Koch: “The SkillsLab is developing into a patient-free teaching hospital. We can train techniques and medical procedures without harming the patient. We have been doing that for quite a number of years for the endoscopy. We train the most basic skills with gastroenterology residents, surgeons, junior doctors and nurse endoscopists.”

He continues: “Of course you can also do this introduction with patients, but that is quite uncomfortable for the patient and also for the trainee endoscopist. Also my pointers during a simulation training are followed better than during a scope with a patient. That is a more stressful situation, which means information does not always penetrate. Thanks to the simulators there is a safe learning environment in which students are allowed to make mistakes and to repeat procedures endlessly.”

Treatment of hemorrhage
Endoscopy simulators are mainly used during the basic training. Koch also arranges advanced courses in the SkillsLab, for instance for the treatment of hemorrhage or the removal of early stage cancer in the gastrointestinal canal. “We have participants from all over the world for those courses.”
Rich tradition of microsurgery

There is a special department within the SkillsLab where surgeons can learn new techniques and practice their operation skills. This deals specifically with microsurgical techniques in which very small blood vessels and nerves are sutured under a microscope.

Erasmus MC has a long tradition of operating under a microscope. In this context the SkillsLab Microsurgery was founded. “We have a good reputation,” says professor Steven Hovius. The head of the department of Plastic and Reconstructive Surgery is one of the founders of the SkillsLab Microsurgery.

“Outside of the Netherlands there are not many institutes with good facilities where you can train as intensively as here,” course leader Ineke Hekking adds. “We have participants from all over the world. Mainly plastic surgeons, but also neurosurgeons, orthopedic surgeons, dental surgeons and trauma surgeons. They not only come to learn how to attach really tiny vessels, but also for more general matters. For instance, how do you treat tissue without causing unnecessary damage?”

Human body

The facilities of the SkillsLab have a huge added value, says Dr. Dennis den Hartog, trauma surgeon for the department of General Surgery / Traumatology at Erasmus MC.

Den Hartog teaches courses in the field of trauma surgery. He says: “Practicing on the bodies of deceased people with instruments and materials is of great importance to surgeons. For a trauma surgeon this mainly involves bones and joints; places that are often damaged.”

The bodies of deceased people, present in the SkillsLab, are the most suitable according to him. “Of course you can use plastic bones to practice placing screws and plates to repair a break. That is fine for the training of basic skills. But if you want to practice how to approach the bone, a plastic bone is not an option. A real bone is not bare, it is enclosed in tissue, with nerves, sinews and blood vessels. The body of a deceased person is the most suitable.”
These are fungi on special culture plates. They can cause Mycetoma, an infectious disease which leads to amputation of the foot in a quarter of patients. The disease is most common in countries such as Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Columbia and Argentina.

Very little scientific research is done on the subject of Mycetoma. This will hopefully change now that the World Health Organization (WHO) has placed Mycetoma on the list of forgotten diseases in 2013. This increases the chances of researches subsidies.

Dr. Wendy van de Sande, researcher with the department of Medical Microbiology & Infectious Diseases at Erasmus MC, is working on the diagnosis and treatment of Mycetoma. Among other things she is exposing the fungi to substances which might inhibit their growth. Her research results may lead to better cures.
Bringing Mycetoma out of anonymity

Attention for tropical infectious disease
Insufficient knowledge of the tropical infectious disease Mycetoma is hindering an effective treatment. Thanks to the official status of ‘neglected disease,’ this might now change.

A quarter of Mycetoma patients need to have their foot amputated. Yet there is little scientific interest in the disease, states Dr. Wendy van de Sande, researcher with the department of Medical Microbiology & Infectious Diseases at Erasmus MC. She says: “Early in 2013 the foremost Mycetoma researchers in the world gathered in Geneva. There were barely ten of us, from Mexico, Sudan and the Netherlands among others. Our goal was for Mycetoma to be officially recognized as neglected disease.”

For it is this lack of recognition that Van de Sande sees as the reason why so few researchers pay attention to Mycetoma. The World Health Organization (WHO) has compiled a list of neglected diseases that are mainly prevalent in developing countries.

Van de Sande: “If a disease is unknown, it will be very difficult to obtain research money. But we did it: Mycetoma was added to the list in 2013. I’m very hopeful that this will increase the chances of subsidies.”

According to the researcher, this is badly needed, because there are many unanswered questions: “We don’t know for example how often Mycetoma occurs. Cautious estimates put the number in high-risk countries at several cases per 100,000 inhabitants, but the true numbers are presumably much higher.” Mycetoma is most common in countries such as Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Columbia and Argentina.

Which micro-organism causes Mycetoma? That question must also be answered. Van de Sande: “If the disease is caused by a bacteria, the chances of a cure are fairly good, because antibiotics are usually very effective. If it is caused by a fungus, treatment with an antifungal medication is normally not sufficient and surgery is also needed. And you can’t simply prescribe any antifungal medication, because not every fungus will be affected.

You have to first identify the fungus in the laboratory, but this is difficult. We want to develop methods to determine quickly and reliably which microorganism is causing the infection. This method can preferably also be executed in the tropics.”

Risk factors
The development of an effective treatment is another important goal. Van de Sande: “Medications are being developed. We have to discover whether these are applicable. In my lab we are researching a better therapy. Among others we are working together with the Mycetoma Research Center in Sudan, the only research center in the world specialized in the disease. The center sends us fungi which we study, for instance examining their sensitivity to new antifungal medications.”

The researchers also want to document the risk factors and ways of preventing the disease. Van de Sande: “Does it help to wear shoes? Should cattle be kept separate from man? Such simple matters have never been properly investigated. This disease has been neglected for so long. If this disease occurred in the Western world, there would already be a cure.”

Bone damage

Mycetoma probably begins with an injury to the foot, for example from a thorn prick.

After this it can take years before the condition manifests itself in the shape of painless spots of infection containing balls the size of a peppercorn. The color of the grains varies and is determined by the cause of the infection: often white or black for fungi and whitish yellow or red for bacterial infections. The center of infection slowly spreads and eventually damages the bone. This leads to problems walking, pain and often amputation of the foot.
Genetic analysis determines treatment

Clarify mechanisms and develop therapies that will become the standard worldwide. That is what the Department of Internal Oncology of Erasmus MC Cancer Institute did for several types of cancer. An interview with department head Stefan Sleijfer.

“The concept of tailored therapy, or personalized medicine, is used so much nowadays that we almost forget that it was very different not so long ago,” says Sleijfer, professor of Medical Oncology.

“Roughly thirty years ago all women with breast cancer received hormonal therapy because research showed that a small number of patients responded well to this. It was discovered later that the therapy works through connective spots, estrogen receptors, which can be found on the outside of the tumor cell. But far from all breast cancer cells have these receptors. A woman with this type of cancer will not be helped by hormonal therapy. Nowadays hormonal therapy is only used on women with breast cancer where the receptor is present. The importance of fine-tuning the treatment is increasingly acknowledged and increasingly possible.”

Profile
At the same time ‘tailored therapy’ does not mean that the treatment will be different for every individual patient, according to Sleijfer. “That is just not possible on a practical level. What does happen more and more is that doctors differentiate between various groups of patients who seemingly have the same type of cancer. Are there similarities in certain characteristics, such as the genetic characteristics of the tumor cells? A certain genetic profile of the tumor cells leads to a specific treatment.”
Thanks to technical developments, scientists are increasingly able to separate tumors into subclasses. Sleijfer: “This used to only be possible based on observations with the naked eye. Then methods were developed to differentiate between cells under a microscope using stains. Nowadays we are able to map the genetic profile of tumors. Especially this genetic analysis has accelerated personalized medicine. We can now determine mutations in the DNA, changes to the genetic information of the tumor cell, which provide clues to the most efficient treatment.”

**Classic or new**
Tailored therapy involves choices: which patient will benefit from a certain treatment and which will not? Sleijfer gives an example: “A melanoma is a type of skin cancer which is based on the pigment cells. Those cancer cells can metastasize to other organs. 50% of patients with melanoma show a mutation (in the BRAF-gene), making them more susceptible to treatment with a new drug. Patients with tumors that do not show the same mutation, do not profit from that new drug. They receive classic chemotherapy. That same BRAF-mutation is also seen in a certain type of intestinal cancer. We are now studying whether this treatment works in patients with intestinal cancer and this BRAF-mutation.”

In the near future drugs will more and more only be given to patients who have a significant chance that the drug will work. And at the time of day and in a dose which is expected to give the best result for that patient (see page 16). Sleijfer: “Therefore tailored therapy benefits the cost effectiveness of the treatment. That is important, because the number of people with cancer is growing, mainly due to the aging population. If we wish to provide good care to everyone in the future, cost control is inevitable.”

**Better survival time**
Will the improved treatments lead to cancer being considered a chronic disease at a certain point? Sleijfer: “I’m very cautious with statements like that. Certainly enormous strides have been taken for certain types of cancer, such as Gastro-Intestinal Stromal tumors (GIST). Professor Jaap Verweij (now Dean and board member at Erasmus MC, ed.) has done a lot of work in this area. GIST is a rare type of cancer where tumors develop in the supportive tissue around the organs, often the stomach or the small intestine. Those tumors have a mutation in the DNA, making them extra sensitive to a certain drug (Imatinib). Thanks to this treatment the average survival time of patients has gone up from nine months to approximately five years. And 10 to 15% of these patients benefits from Imatinib for over ten years.”

But GIST is not representative for all types of cancer. Sleijfer: “GIST are relatively ‘dumb’ tumors. They often only have one motor driving their cell division. If you can disable this motor, with Imatinib for instance, this immediately has huge consequences. Most other tumors are not so easy to deal with. They are built up from many different tumor cells with very varied characteristics. A tumor is often a collection of tumor cells with different motors driving the cell division. One drug can kill a part of the cancer cells, but other cells survive: they have mechanisms which allow them to escape and which allows the tumor to spread, in spite of a treatment that was initially successful.”

**Adapted**
Sleijfer’s ambition? “A cancer treatment like we apply to HIV. There the therapy is tuned to the mutations shown by the virus particles. The therapy is adapted to each new mutation. A combination therapy tackling various mutations simultaneously is the most effective. But there is an important difference. An HIV-virus particle is totally foreign to the human body and genetically much simpler than a tumor cell. A cancer cell stems from a body cell and therefore has many characteristics inherent to the body. That makes it a lot harder to find a therapy that only targets the tumor cell.”

**Progress**
The Department of Internal Oncology has made a significant contribution to the progress in patient treatment. Sleijfer: “For instance in the area of breast cancer, ovarian cancer, GIST, testicular cancer, prostate cancer, soft tissue tumors and esophageal cancer. We have clarified mechanisms and developed therapies which are now the standard worldwide. The same goes for other departments within Erasmus MC which are active in the field of oncology. Take prostate cancer screening and colonic cancer screening for instance, and the treatment of acute myeloid leukemia, multiple myeloma and brain tumors.”
Treat and fight

The field Stefan Sleijfer works in aims at the medicinal treatment of cancer patients. This includes both the actual treatment of the tumor and the fighting of the symptoms. Internal Oncology is working on therapies such as chemotherapy and more tumor-specific methods.
A breakthrough under reservation

In 2014 researchers of the department of Hematology unraveled a very serious form of acute myeloid leukemia and published about it in Cell. A breakthrough, says research leader professor Ruud Delwel, although he does warn against too much optimism.

What is so special about the discovery? Professor of Molecular Leukemogenesis Ruud Delwel: “We not only cleared up the mechanism that lies at the basis of a very serious form of acute myeloid leukemia, but we have also discovered a possibility of effectively treating this form in a culture dish using certain molecules. We still need to study how these methods will work on a patient.”

Upgrade
Delwel initially sent the manuscript documenting his findings to Cancer Cell. But the editors saw the importance of the findings and chose an 'upgrade' to Cell, which is rare. The origins of Delwel's recent discovery go back some twenty years, when he went to do research in Memphis, USA. "My boss at the lab, professor James Ihle, had published an article in Cell shortly before I arrived. It concerned the discovery of a new gene in mice with leukemia: EVI1. The EVI1 gene is active in the stem cells in bone marrow, but is switched off once the stem cells develop into other types of cells. At least, that is what should happen, but in a certain type of leukemia the EVI1 gene remains active."

By now Delwel is specialized in acute myeloid leukemia (AML), a type of leukemia which occurs mainly in adults. He recounts: "AML can be divided into subtypes with the same deviation in the DNA. There is a small group, only 2% of AML-patients, with a deviation in chromosome 3. A part of their DNA has broken off and been rebuilt backwards. The result: EVI1 becomes active. We wanted to know how this was possible."

Fatal
Delwel urges to unravel the mechanism behind this specific form of AML is not a coincidence: "Due to our knowledge of underlying causes we are now able to cure certain subtypes of leukemia. But the prognosis is not good for people with this specific deviation in chromosome 3. The disease is fast and fatal."

The first step of the study was to determine what happens to cells when the EVI1 gene is switched off. It turned out that cells that were cultivated in the laboratory stopped dividing at an explosive rate and continued to develop normally. This points towards an important role of EVI1 in the growth and development of the leukemia cells.

In acute leukemia the development of stem cells into healthy blood cells is disturbed: the bone marrow and the blood show a proliferation of unripe white blood cells, so-called blasts. Can the proliferation of blasts in patients be prevented by switching off EVI1? Delwel warns against too much enthusiasm: "Of course these findings are important, but the cultivated cells are no more than a model. You cannot translate the findings directly onto the situation of a patient. But this does not mean models are not of vital importance in discovering mechanisms which could eventually lead to a good therapy."
‘One error in rebuilding, with two consequences on the gene level and dramatic consequences for the patient’

**Acute leukemia**

- There are two types of acute leukemia: acute lymphatic leukemia, which mainly occurs in children, and acute myeloid leukemia, which manifests mostly in adults.
- Acute leukemia is rare. In the Netherlands for example it is diagnosed in four out of 100,000 people every year. In the US five out of 100,000 people.
- The precise cause is unknown.

**Errors occur constantly**

In healthy people the EVI1 gene is switched off as soon as the stem cell develops into a ripe blood cell. With patients with this subtype of AML this does not happen and EVI1 remains active. Why is this?

Delwel: “Errors occur constantly in the DNA, for instance because of the radiation of the sun, because of what we eat or drink or because of certain chemicals. The body is constantly working to repair these errors, but sometimes this goes wrong. That is what happens in this subtype of AML, where there is a break in chromosome 3. This break has two important consequences. At the one breaking point is the GATA2 gene. This gene is normally switched on, under the influence of an activator, an attachment point for certain proteins. At the other breaking point is the EVI1 gene, which is normally switched off. In this type of AML patient, the piece of chromosome 3 is rebuilt in the wrong way. This causes the activator to be located near the EVI1 gene and far away from the GATA2 gene. The result: GATA2 has lost its activator and is switched off, while EVI1 is switched on. One error in rebuilding, with two consequences on the gene level and dramatic consequences for the patient, because the result is an unchecked growth of unripe blood cells.”

**Different context**

Delwel and his colleagues discovered more.

He says: “Due to the reversal of the piece of chromosome 3, the activator of GATA2 does not only move to EVI1, but it also ends up in a different DNA environment, in a totally different context. And this offers unexpected opportunities to switch off EVI1. As it turns out, certain medications (so-called BET-inhibitors) are able to stop the activator in this different context. And this happens very specifically, because when the activator is in its normal place near GATA2, these medications have no effect.”

How to proceed? Delwel: “We now know that it happens, but we don’t know exactly what it is that happens. We see that the BET-inhibitors work, but we don’t know precisely how. And we also want to learn more about EVI1, because the exact role of that protein is still a mystery. It would be wonderful if the combination of that knowledge would lead to an efficient therapy to combat this form of leukemia.”
Better and safer brain surgery

Medical 3D-technology on the rise

Neurosurgeon professor Clemens Dirven dreams of 3D images in the operating theater. “How great would it be if I could see exactly what I’m doing in the skull in 3D during brain surgery?”
Better and safer brain surgery

The first steps were taken a few years ago. Erasmus MC is one of the few hospitals in the Netherlands to have a space where three-dimensional images can be shown and manipulated: the I-space. This space – with smooth black walls and floor – is located in the department of Bioinformatics of the research faculty of Erasmus MC. Visitors can enter wearing special slippers and 3D glasses. Computer menus are projected on the wall and can be operated using a kind of laser gun. There is a three-dimensional image of a head floating in the back of the space. You can walk around it and examine it from all angles.

Menu and click
Project leader Dr. Anton Koning explains that a dark spot on the anterior left of the pictured skull for example is the hole where the surgeon has drilled into the skull. He moves his ‘gun’, clicks the menus on the walls and look: the head is bisected. You can now see the tunnel the brain surgeon once made to be able to remove a tumor. A few more clicks on the walls and odd spots along the edges of the hole become visible: leftover pieces of cancer tissue. Koning: “Those leftovers have practically grown into the blood vessels. The surgeon was unable to remove them from fear of damaging the blood vessels. This is what eventually killed the patient.”

Surgery preparation
So this is not yet an operating theater, but a kind of research lab. Dirven is enthusiastic. “This is the first step. The great thing is that we can use the I-space to prepare properly for complicated brain surgeries. We for instance look beforehand how the tumor can best and most safely be removed from the brain. The view you have with a three-dimensional image is much better than with a normal flat screen. The I-space allows us to examine it from all angles and see where the arteries lie that we really cannot touch. The better the technology, the safer the surgery.

Embryos
The I-space also serves a research purpose. Professor of Bioinformatics Peter van der Spek uses the I-space to document the development of embryos. This knowledge helps him understand why cancer cells grow. There is a sudden growth of cells both in cancer and in a fetus. But in cancer the genes are switched on at an unwanted moment. Cells suddenly begin to divide when they shouldn’t. Something in the gene population goes wrong and produces a DNA mutation. The trick to Van der Spek’s research is that he hopes to use the data from the fetal study to understand which genes or groups of genes make that mistake. If he knows which group of genes are responsible for the growth of certain cancer cells, then doctors have something to base a therapy on. The same goes for brain tumors. Dirven: “There are drugs which help fight cancerous growths which have been caused by certain groups of genes. If we know which type of cancer is caused by which group of genes, we can look for the fitting drug.”

Van der Spek is compiling large files of data and studying these. Just as in the I-space, this requires the most advanced information technology. Dirven: “Doctors and technicians can achieve a lot together.”
In a competition in honor of the centenary of the Radiological Society of North America, this image was chosen from 137 submissions from all over the world. The creator: Dr. Marius de Groot of the Departments of Radiology, Medical Computer Science and Epidemiology of Erasmus MC.

De Groot: “We see the brain of a 72-year old participant of the Rotterdam Study (Erasmus Rotterdam Gezondheid Onderzoek, ERGO), a large study among people of 45 and older from the Rotterdam neighborhood of Ommoord. The grey matter of the brain has been made transparent, giving us a direct view of the white matter, the connective pathways of the brain. The image was created using an MRI scanner. Thanks to images like this we can study the changes to the brain caused by aging. Information on these changes contributes to insight in the development of diseases like dementia.”
ENCORE joins forces

Man and mouse steam ahead

Improving the quality of life for patients with hereditary (congenital) developmental disabilities in learning and cognitive abilities. That is the goal of ENCORE: Erfelijke Neuro-Cognitieve Ontwikkelingsstoornissen Rotterdam, Erasmus MC (Hereditary Neuro-Cognitive Developmental Disabilities Rotterdam, Erasmus MC).

“It cuts both ways. The expertise within ENCORE provides the patient with a rare congenital disorder with the most optimal care. And because the affected gene has been identified, we can perform extremely focused laboratory studies into the underlying mechanisms and translate this back to the clinic.” According to Ype Elgersma this is the basis for high-level academic care and research within ENCORE. Elgersma is professor of Molecular Neurobiology and scientific director of ENCORE.

Multidisciplinary

ENCORE is a multidisciplinary expertise center in which specialized out-patient clinics work closely together with research groups. They have set their sights on hereditary (congenital) cognitive developmental disabilities. These patients have impaired cognitive functions, but other functions are often also less developed: walking, breathing, the eyes, the heart, et cetera.

Professor Henriette Moll is pediatrician and assistant director of General Pediatric Medicine at Erasmus MC-Sophia. She says: “The goal of ENCORE is to improve the quality of life for patients with hereditary (congenital) cognitive developmental disabilities. This is done through specialized care and research. The research is both fundamental (what is the role of a certain protein in the brain cells?), clinical (how does the disorder develop over time and what treatment is best?) and translational (which discovery from the laboratory can we apply in this clinic?). This
approach should lead to a better diagnostic (how do you recognize the symptoms of a certain disease?) and better treatment methods."

The following departments are involved with ENCORE: Pediatric Medicine, Pediatric Neurology, Pediatric and Youth Psychiatry/Psychology, Psychiatry, Clinical Genetics, Neurosciences and Radiology.

**Collaboration**

When ENCORE was founded in 2011, the research into hereditary neuro-cognitive developmental disabilities (brain deviations in learning and cognitive abilities) was still focused fully on mice. But the need to work together with doctors from the clinic soon arose.

Elgersma: "We had seen that mice with Neurofibromatosis (NF1) improved immensely when we gave them a certain medicine (simvastatin). Of course we wanted to know if the same medicine would also have a positive influence on children with the same syndrome." Elgersma contacted the department of General Pediatric Medicine, which had been running an NF1 out-patients clinic for more than 25 years. This clinic has grown into the national expertise center for children with NF1. Here all patients are seen by a pediatrician, a pediatric neurologist, and other specialists when indicated. By now two studies involving these children have been completed.

Moll: "Many children with NF1 have learning difficulties, but also problems with behavior,
memory, attention and spatial awareness. Mice with the same genetic change as NF1 patients showed that the medication simvastatin can reduce the learning difficulties. But the two patient trials showed that it does not work on humans. We are now looking for other medicines which tackle the mechanism in a more targeted manner. A third study has recently started with the NF1 patients. We are studying one of these new medicines: lamotrigine."

She continues: “There are also currently two studies involving children with TSC which research the effects of rapamycin. We are investigating whether this medication can suppress serious epileptic attacks in children up to the age of four. And with children older than four with TSC we are studying whether there is an improvement in cognition and autistic traits.”

The same symptoms
The clinic and the lab constantly feed each other with insights and questions. The lab is searching for the mechanisms behind the diseases. Which proteins are involved with the processes in the brain cells? And where does it go wrong with the various syndromes? To answer these questions, mice are being used which have been altered genetically to such an extent that they show the same symptoms as the children. The doctors take the insights into the mechanism back to the patients: do the processes which were found in the mice, also play a part in them? On the other hand observations from the clinic are tested in the laboratory.

Moll gives an example: “The Angelman outpatient clinic is currently monitoring about eighty children. Their symptoms are studied and documented. They are often struggling with eating disorders and obesity. Research on mice in the lab is trying to find out why this is.”

Active role
“The need to pool the knowledge from the lab and from the clinic is strengthened by the express wishes of the patient associations,” Elgersma relates. Patient associations play an active role, for example by submitting research questions. Moll: “Sleep disorders are common in children with Angelman syndrome. At the request of the Dutch patient association we are looking for explanations and solutions, such as adapting the sleep ritual.” Elgersma: “And we are also looking at our mice models and seeing disturbances to their sleep behavior there too.”
Dealing with doom scenarios

From local suffering to global disaster. From a relatively small number of casualties to millions of dead. The Department of Viroscience at Erasmus MC is one of the main players in the world trying to prevent these scenarios after new and unknown viral infections crop up.
Ebola

Emergency aid in West Africa. That is what the Department of Viroscience at Erasmus MC offered on the spot in late 2014 and early 2015 after the Ebola outbreak in Guinea, Liberia and Sierra Leone.

Department Head Marion Koopmans: “We set up three laboratories. These tested whether people had Ebola and whether deceased people had died of this viral infection. The labs were manned by Dutch people we had trained. We are now trying to pass our expertise on to local health workers, after which we will stay involved as consultation center.”

Erasmus MC is working in West Africa at the request of the World Health Organization. The Department of Viroscience is the consultation center of the WHO for viral hemorrhagic fevers, some of the most dangerous viral infections.

Measles

Vaccination against measles turns out to have a double positive effect. It of course prevents direct death from measles. But because this disease does not occur, the immune system is also not weakened over a long period and there is not a heightened risk of death from other infectious diseases.

This was announced in the spring of 2015 by researchers of the Department of Viroscience at Erasmus MC and colleagues from Princeton University, USA. They showed that the measles have a long-lasting effect on the immune system. Until recently it was believed that measles suppressed the immune system during several weeks or months, but the researchers proved that children who have suffered from measles can still die from infectious diseases more than two years afterwards, due to a weakened immune system.

The researchers published an article on the subject in the scientific magazine Science. Measles researcher Dr. Rik de Swart was involved on behalf of the Department of Viroscience at Erasmus MC.
Being the first institute in the world to demonstrate in 1997 that the H5N1-influenza virus - the bird flu virus - can indeed transfer from bird to human. Working with other organizations in 2003 to ensure that the SARS-corona virus causes no more than one thousand deaths and thereby preventing a pandemic. Identifying the MERS-corona virus in 2012, when the virus has already caused the deaths of dozens of people in the Middle East, and thereby laying the foundation for the development of a vaccine.

Just a few of the many results the Department of Viroscience of Erasmus MC has achieved. In the past twenty years ‘Rotterdam’ has discovered about fifty new viruses in humans, pets and wild animals.

The world as village
“In all modesty I can say that our Department belongs to the international top when it comes to discovering new and unusual viral infections, or emerging infections.” So says Department head and professor of Virology Marion Koopmans. “In the past ten to twenty years it has become an increasing challenge to do this quickly. Nowadays the world is a village. Numerous people travel the world by plane every day. Our belongings travel with us, mosquitoes travel with us and viruses travel with us. More and more we are confronted by infections that spread quickly and no longer stay contained within a small part of the world. In the past you could spend years doing research, but now it is necessary to cram a lot of steps into a very short timeframe. What is this unknown disease? What can you do to fight it?”

Predict
The Department of Viroscience won global fame by responding adequately to new viral infections. The culprit was identified and this was the basis for the development of a vaccine. These activities obviously remain at the top of the list of priorities. “But in the coming years we also want to become increasingly able to predict,” says Koopmans. “When you know from which area you can expect the biggest problems, you might be able to prepare yourself by for instance creating new vaccines and treatments.”

So how do you predict? Koopmans: “At this moment we are researching all the phases in an outbreak. This is mainly aimed at infections that pass from animals to humans. How does this work? For example, what happens when people cut down forests and start farming an area, putting wild animals in places they were not in before and perhaps living close to humans? What are the barriers that prevent viruses from passing from animals to humans? And what are the possibilities? Why does one virus successfully transfer and the other does not? And if a human is indeed infected, under which circumstances does this lead to major health problems? When does this one person himself become a source of infection for other people? Which factors decide whether the virus spreads slowly or quickly?”

She summarizes: “We are developing a box of tricks for each of these steps so that we can determine quickly and at an early stage how serious it is and how far it has already spread. When we gain insight into all these determining factors and begin to recognize patterns, we will know earlier and better what to do to combat new viral infections.”

Common goal
Koopmans emphasizes that the Department of Viroscience at Erasmus MC cannot achieve this alone. “Networking and collaboration are very important. After the SARS-outbreak the largest virological institutes in the world came together to achieve a common goal. If we do this again, we can accomplish a lot in the next decade.”

Erasmus MC also supports collaboration with smaller parties on a local level. Koopmans: “We are for instance part of PREPARE: Platform foR European Preparedness Against (Re-)emerging Epidemics. This is a network of about 900 hospitals who are tasked to be prepared for a large viral outbreak. In that moment we have to be able to rapidly answer the most important questions in order to fight the outbreak and treat people. An apparently simple question - how serious is the infection? - proved very difficult to answer in previous outbreaks, while the answer to this question determines the scale of the threat and the needed level of response. In this project hospitals are prepared for an emergency investigation into these vital questions, but also into methods of treatment.”

Also general labs
Talking about international collaboration Koopmans also mentions Horizon 2020: the European Committee program to stimulate European research and innovation. She says: “Together with a group from the Technical University of Denmark (DTU) in Copenhagen we received a subsidy to develop a central system to track and trace outbreaks earlier and better. This has been accomplished through analysis of the genetic information of pathogens. We use the latest molecular techniques and bioinformatics analyses, which are developed in such a way that they become suitable for less experienced users. It is our goal that local labs all over the world can use this and thereby help to trace outbreaks.”

For more information visit www.compare-europe.eu.
Warm chemo as powerful weapon

HIPEC, irrigating the peritoneal cavity with heated chemotherapy, is a new treatment at Erasmus MC Cancer Institute. This is used to fight metastasized colonic tumors in the peritoneum. The therapy has doubled the survival time. Some patients have even been cured completely.

Oncologic surgeon Dr. Pim Burger is one of the three doctors in Erasmus MC who have been trained in the HIPEC procedure. He explains the importance of the treatment.

“Colonic cancer often metastasizes to the peritoneum. The peritoneum is only a single cell layer thick, but if you were to spread it out, it would cover a surface of several square meters. It encompasses all the organs in the abdomen and ensures that the organs can move freely in relation to each other. Tumor cells can nestle in the peritoneum. It often concerns hundreds or even thousands of tiny specks. Anything we can see with the naked eye is removed surgically, but we assume that this does not remove everything. There are still loose tumor cells roaming around the abdomen after a surgical procedure. The heated chemotherapy is important in destroying these non-visible tumor cells.”

Expertise
Erasmus MC was already able to help patients with colonic cancer which has metastasized to the liver, the lungs or to more unusual spots. The University Medical Center also has the expertise to provide care to people with large colonic tumors which have not metastasized, but with grow into other organs. And now they are also able to help patients with cancer that has metastasized to the peritoneum.

Burger: "Thanks to our multidisciplinary approach, which includes surgeons, oncologists, radiotherapists and radiologists, we are able to form a treatment plan which is completely tailored to the individual patient. Erasmus MC is a frontrunner in this field. For the treatment of the patient with metastasized colonic cancer, we are at the top of what is possible. And the HIPEC treatment is now also one of the options."
The HIPEC method is effective. Colonic cancer which had metastasized to the peritoneum was previously untreatable. Patients died within the year.

Burger: “HIPEC has doubled the survival time. Some patients have even been cured completely. But I expect more can be achieved. Together with the Antoni van Leeuwenhoek Hospital in Amsterdam we are going to study how we can optimize the method. This could include using certain types of chemotherapy, which are specifically aimed at the individual patient. The chemotherapy which is used as follow-up treatment after HIPEC, can also be optimized. And we plan to study whether preventative irrigation of the abdomen is of use to people with an increased risk of cancer metastasizing to the peritoneum. Sometimes preventative irrigation is possible through a small opening in the abdomen, just like in keyhole surgery.”

**Sensitive to higher temperatures**

HIPEC stands for Hyperthermic IntraPEritoneal Chemotherapy. The abdomen is irrigated with heated chemotherapy.

**The procedure**
- The abdomen is opened up completely.
- All visible tumors are surgically removed.
- The abdominal wall is pulled open. This creates a kind of basin, in which five to seven liters of irrigation liquid is pumped round.
- The liquid is heated to 42 degrees Celsius (107.6 degrees Fahrenheit). The chemotherapy solution is added to this. The irrigation takes 90 minutes.
- All the damage caused by removing the tumor is repaired. The abdomen is closed.

**The advantages**
- The raised temperature ensures that more cancer cells are destroyed. Cancer cells are often sensitive to higher temperatures.
- The organs in the abdominal cavity are treated from the outside and the chemotherapy only penetrates several millimeters. This can be enough to destroy small metastases. Because the chemotherapy is not administered through the blood, the dose can be increased. This increases the effectivity. In the blood a high dose is more likely to lead to toxic side effects.

**Other applications**
HIPEC can not only be used for the treatment of metastasized colonic cancer, but also for peritoneal metastases of mesothelioma (asbestos cancer) and mucinous tumors of the appendix (pseudomyxoma). Patients suffering from the latter condition often live decades longer thanks to the therapy.
Dr. Kim van der Heiden got involved with research for the European Space Agency ESA. What does a vascular biologist do for the European Space Agency?
In atherosclerosis atheroma are formed: an accumulation of a fatty substance in the artery wall. This greatly reduces the elasticity of the artery wall. The atheroma can completely clog up the artery or cause it to tear.
Within the laboratory for Biomedical Engineering of the Department of Cardiology we study biomechanical forces on the walls of blood vessels. We mainly do this for atherosclerosis, where degenerative material has accumulated in the inner wall of the artery to form an atheroma (see frame, ed.). Flowing blood exerts friction on the artery wall. The artery wall also expands due to the blood pressure. The endothelium cells, the cells on the inside of the arteries, are very sensitive to this. I create endothelium culture, let liquids flow over them and see how they react to this.

**Porto**
Due to my experience with endothelium cells and biomechanical forces I was asked to evaluate a research proposal. This had been submitted to ESA by three masters students, a doctorate student and a professor of Bioengineering from Porto. After the project had been approved, I started to coach the applicants. The students did the experiment in The Netherlands. The town of Noordwijk has a large ESA centrifuge. Selected student are able to study the effects of elevated gravity there. ESA is interested in this, because astronauts are exposed to elevated gravity during the launch of a rocket. The students from Porto exposed endothelium to 3g and 10g forces (three and ten times our own gravity respectively, ed.) during four or sixteen hours. They then let the cells form blood vessels in a three-dimensional gel. It is not yet known whether the experiment has produced valuable results.

**Leads**
The forces which affect the cells in a centrifuge are different than the natural forces. Yet this research is also interesting to me. The biological routes which are switched on by the centrifugal forces in the cells also play a part in the processes I study. Hopefully the results will provide leads for further studies. This study is especially interesting to tissue engineering. This involves laboratory techniques in which tissues or organs are created using cells and biomaterials. We mainly aim at the formation of blood vessels from cultured cells. These could for instance be used in patients with atherosclerosis to replace a piece of the artery which has been constricted by atheromata. We currently use stents in these cases to hold the vessel open. Or a bypass is created using a blood vessel from a different body part. The greatest challenge in creating a cultured blood vessel? The circulation of that blood vessel by micro-vessels. It is not difficult to coat a polymer tube with cells, but there also have to be little blood vessels running through it to provide the cells with nutrients and oxygen. The experiments in the centrifuge study whether the growth of these micro-vessels is improved.”
Bio-absorbable internal carrier of medicine

The ultimate stent

‘More and more the diseased blood vessel will be healed from the inside using the stent’
A stent keeps a constricted blood vessel open, but compared to an angioplasty it has the disadvantage that tissue growth is more common and the blood vessel can still become constricted. The risk of thrombosis is also increased in the period of 24 hours to three weeks after the stent has been placed. Dr. Heleen van Beusekom has been researching improvements since the late eighties.

“My first laboratory studies at Erasmus MC were aimed at the problem of thrombosis,” says Dr. Heleen van Beusekom. “We studied various types of stents, because the material used to make the stent is of great influence on the developing of thrombosis. In the same period we also experimented with the first medicinal stents. These have a layer of heparin for instance, which slows the clotting of the blood and so decreases the chance of thrombosis.”

Inflammation
This led for example to the knowledge that a stent made of polymer can cause severe inflammations in the blood vessel. The first drug-eluting stent, which releases medication during several months after placement to keep the scar on the blood vessel nice and thin, was also coated in a thin layer of polymer. Van Beusekom: “We now believe that those polymers, even in small amounts, can still cause problems once the medicines have disappeared from the stent. That is also why you must always examine whether the ‘carrier’ of a drug-eluting stent (the tube without the medication, ed.) does not cause serious reactions.”

Naturally occurring substances
What is the state of affairs? Van Beusekom: “We now have metal stents of which the coating is naturally absorbed by the body. The ultimate stent will be fully bio-absorbable when it has done its work, but we still have a long way to go before all patients can be helped by these. We are working on stents that are made of substances naturally occurring in the body, such as lactic acid. These will be absorbed by the body within several years. I expect more of these developments in the future. Patients now take medication to control the hardening of the arteries. I think that in time we will also be able to incorporate those medications into stents. More and more the diseased blood vessel will be healed from the inside using the stent.”
Better view of tumor with new technique

More accurate cutting

Preventing patients with cancer in the head and neck area who have had surgery from having to be operated on again, or needing another supplementary treatment. Stijn Keereweer hopes to contribute to this through fluorescence image-guided surgery.
‘Fluorescence image-guided surgery already successful in lab animals’

Seeing with the naked eye and feeling with a practiced hand. Once in the operating room, an experienced head and neck surgeon has no more than this to judge whether tissue is healthy or cancerous. Based on this observation the specialist decides which area to remove. Unfortunately this is not a foolproof method as for example in one in four tongue surgeries it is found later that not all the cancerous tissue has been removed. The patient must then undergo another operation or supplementary treatment in the form of radiation or chemotherapy.

Stijn Keereweer took up the challenge to make more accurate observations. He was a resident in training to Ear, Nose and Throat doctor – the first step in the specialization to ear, nose and throat surgery or otorhinolaryngology. In 2014 he got his degree cum laude based on a study which showed that images of the borders of tumors can be shown in real time in the head and neck area of lab animals. The next step should be to apply this to humans. This is expected to be possible in a few years.

**Expertise**

Keereweer relates that his study was born out of the need for more accurate surgery among head and neck surgeons at Erasmus MC, and is thanks to the expertise in the area of fluorescence image-guided surgery at the Leiden University Medical Centre (LUMC). “Professor Clemens Löwik of Erasmus MC and Dr. Alexander Vahrmeijer of the LUMC are prominent researchers in the area of fluorescence image-guided surgery, a way of surgically removing cancerous tissue more accurately. I asked them: do you also apply this in the area of head and neck oncology? The answer was no. You can’t study everything at once, in Leiden the focus for the moment is on types of cancer which impact greater groups of patients. Such as breast cancer, colonic cancer and prostate cancer. I then suggested studying this technique as applied to cancer in the head and neck area.”

**Near-infrared**

What is fluorescence image-guided surgery exactly? Keereweer: “My research looked at tumor-specific substances. You inject these into the blood stream as a liquid and then they only attach to tumor cells and not to the surrounding healthy tissue. The color cannot be seen with the naked eye, because we use a specific type of fluorescence which is close to infrared and cannot be registered by eye. But this is possible with a camera developed by LUMC and the Harvard Medical School. During surgery, when there is an open wound, you position the camera over the surgical field. Thanks to certain filters the camera is capable of extracting the light from the tumor cells and projecting this image on a screen.”

**Screen**

According to Keereweer a huge advantage is that the surgeon can see what is happening live: while the specialist is doing his work, he can use the screen to see what is cancerous tissue and what is healthy tissue. “There are many ways of determining whether someone has cancerous tissue before the operation, and where this is located. For the tongue you would use an MRI for instance. But once you are in the operating theater, you can only touch and see the actual tissue of the patient. For example, cancerous tissue feels firmer than healthy tissue. In spite of all the expertise and experience of our surgeons, this turns out to be more difficult than you would hope. Reality proves that often not all cancerous tissue has been removed. Of course in theory you could have the radiology department make new pictures halfway through an operation, but this is impractical. Fluorescence image-guided surgery allows you to see which type of tissue you are dealing with and what your hands are doing while you are in the operating theater.”

**Application**

Fluorescence image-guided surgery has proved possible in mice, this still has to be shown in humans. Keereweer does not want to raise expectations too high. “We are developing a new tool for the surgeon to better decide where the borders of the tumor are. But I don’t expect this to solve everything. Cancer is sneaky, it can spread out through a thin blood vessel or nerve somewhere deep down for instance. You might not be able to capture this thin line on camera. I hope and expect this technique to prevent supplementary procedures, but this will presumably not be effective in all cases. Operations in studies must prove how much is to be gained from this.”

Medical Delta

Achieving breakthroughs in medical sciences and health care. With this goal in mind Erasmus MC, the Leiden University Medical Center (LUMC) and the Technical University (TU) Delft have joined forces. They do this under the name Medical Delta. The promotional research of Stijn Keereweer is part of this.

www.medicaldelta.nl
‘Quick and efficient where possible, and using all our expertise where necessary’
Quality care with
dependence

Quick and efficient where possible. But using all the needed and extraordinary expertise where necessary. That is the core of the Academic Breast Cancer Center Erasmus MC-Havenziekenhuis, which opened officially in 2014.

It's easily said: one center to treat all women with breast cancer. But one form of breast cancer obviously does not compare to another. Not every patient requires the same care. At the Academic Breast Cancer Center Erasmus MC-Havenziekenhuis they are immediately selected for the most fitting treatment, says Dr. Linetta Koppert. She is an oncological surgeon specialized in breast cancer and is one of the founders of the center, a collaboration between Erasmus MC and Havenziekenhuis Rotterdam.

Dreaming of children
She says: 'At the threshold we decide who enters through which front door. A young woman who dreams of having children and runs the risk of becoming infertile through chemotherapy, is treated at Erasmus MC. This is often a case of a very invasive disease with huge consequences for the patient. Such patients need the maximum care which Erasmus MC, a university medical center, can provide. But a woman who discovered a spot on her breast during the national screening can be treated at Havenziekenhuis Rotterdam, a general hospital. There she will be operated on as soon as possible. The treatment decisions are always taken in a joint multidisciplinary meeting. That is the core of our center: quick and efficient where possible, and using all our expertise where necessary.

Increased risk
Apart from 'selection on the threshold', the multidisciplinary meeting is a trump card for the center. Various disciplines work together: oncological surgery, internal oncology, plastic surgery, radiotherapy, clinical genetics, pathology, psychology, nursing.

Koppert: 'We see each other a number of times a week. A patient will be presented at a meeting, for instance a young woman whose mother developed breast cancer on one side at forty and on the other side fifteen years later. The young woman is wondering whether she should be tested for a genetic disposition to breast cancer. Together we will look at her family tree and see that her mother’s cousin also had breast cancer at an early age. In that case there is a realistic chance that the young woman runs an increased risk of breast cancer due to a genetic mutation. She will be referred to a clinical geneticist who can determine whether this is indeed the case. If the woman turns out to be the bearer of a risk-gene, the most suitable treatment must be chosen: operation, radiation, chemotherapy or a combination. But there are other decisions to be taken. Does the woman wish to partially keep her breasts and is a breast reconstruction needed? And is this possible? The plastic surgeon plays an important part in these decisions.'
Looking for tumor patterns

Attempting to prevent the recurrence of tumors using chemotherapy or anti-hormonal therapy. Trying to extend the lifespan of terminally ill patients with metastasized breast cancer and putting the quality of life first. These are important goals for the Academic Breast Cancer Center Erasmus MC-Havenziekenhuis.

The team includes resident oncologist Dr. Agnes Jager, specialized in the treatment of patients with breast cancer, and Dr. John Martens, researcher at the department of Internal Oncology.

The latter says: “Our department is like a spider in the middle of the web, which also consists of radiotherapists, surgeons, radiologists, pathologists, nurses and plastic surgeons. The mapping of all genetic changes which are being observed in the breast cancer cells is currently being worked on around the world. We are involved with BASIS, a large international study which is led by the British Welcom Trust Sanger Institute. Various labs are collaborating to collect as much information as possible on about 1500 breast tumors. In time this information will certainly influence treatment.”

Behavior and sensitivity

Jager elaborates: “We can learn a lot from pieces of tumor tissue, but also from blood. For instance on the behavior of cancer and the sensitivity to radiation or chemotherapy. It was discovered twenty years ago that women with a mutation in the genes BRCA1 or BRCA2 run an increased risk of breast cancer. But for most of them (roughly 70%) we still can’t find the mutation causing this. We are now mainly searching for the collaboration between small variations in the DNA, which together could increase the risk of breast cancer. Women with this genetic profile could have extra screenings for instance, just like we already do for women with familial breast cancer who are the bearer of a BRCA1 or BRCA2 gene mutation.”

More aggressive

According to Martens each tumor is unique. He shows a chart with hundreds of breast tumors. Behind each tumor is a block signifying a change in a particular gene. Sometimes this is just one gene, sometimes there can
‘Prospects for a target attack using medication’
be six, but each tumor has a unique pattern of blocks and is different from all other tumors. Martens: “But I don’t think we need a completely different therapy for each tumor. Often the important ‘routes’ the cell uses, for instance to multiply, can be tackled with the same therapy. We look for patterns, for something multiple tumors have in common. This opens up prospects for a targeted attack using medication.”

Jager: “I don’t rule out that we will distinguish fifty or sixty subtypes of breast tumors which we each treat in their own way. But also the monitoring, following the tumor during treatment, will become more and more important. If we see that the behavior of the tumor changes during the course of the therapy, we can take this into consideration.” And the fact that a tumor can change over time was confirmed by Martens’ lab: “We discovered an enzyme that can mutate the DNA in breast cancer cells. This causes the tumor to become more aggressive. It can for instance make the tumor cells insensitive to Tamoxifen, a drug that can halt the growth in many breast cancer cells. Because of this mutation and the resulting insensitivity, doctor and patient lose one way of fighting the cancer. We are now studying whether a future therapy could consist of stopping that enzyme.”
In tailored oncology therapy it’s all about drugs which tackle the specific derailed mechanism in the cells of the patient. Professor of Molecular Radiation Genetics Roland Kanaar tells of the search for tailored therapy.

In the past a biopsy would be performed on a breast cancer patient, in which a piece of the tumor was removed. The pathologist would then identify certain characteristics through the microscope. Patients were divided into groups based on these results. Roland Kanaar: “Based on experience they would say: ‘This tumor looks like this, so this is the best treatment.’ But that is a very rough differentiation.”

Nowadays Kanaar and his colleagues try to discover what is happening on a molecular level and how they can tackle this. “We look at the DNA of the cancer cells and at the proteins that are coded by that DNA. We look closer and closer, so that the patients can be subdivided with increasing accuracy. Once you have gathered enough knowledge, you can achieve personalized medicine.”

He continues: “Personalized medicine only works if you know enough about the patient and about the disease. With cancer there is a mechanism which has derailed in the cell: a certain brake has gone or an activating route has been switched on, so that the cell is driven to divide and to grow into a clump of cells. If cancer cells are dependent on this derailment for their growth, then that might also be their Achilles heel. In tailored therapy you look for the medicine which specifically targets that derailed mechanism.”

**Breaks**
Our DNA is an enormously large molecule. Stretched out and laid out it is about two meters long. It consists of two strands which are wrapped around each other. The DNA is constantly damaged, for instance by oxygen, which we have to breathe to stay alive. Oxygen causes around 50,000 DNA-breaks per cell per day. No big deal. It concerns breaks in one of the two strands. These are easily repaired by PARP, a specific DNA-repair protein.

Kanaar: “In many cancer cells the mechanism that is supposed to repair DNA damage is faulty. You can strike hard at the cancer cells by treating patients with a combination of chemotherapy - which causes DNA damage in dividing cells - and PARP blockers, which suppress the damage repair in cancer cells.”

**Bad defense**
Cancer cells which are treated with PARP blockers do not give up easily. The breaks in one of the two DNA strands become a break in both strands. Kanaar: “That kind of DNA damage can be repaired by another DNA repair system. BRCA proteins are part of that repair system. A special group of breast cancer patients has a mutation, an error, in the BRCA1 or BRCA2 gene which codes these proteins. In this group of patients the tumor cells, but not the healthy body cells, are not capable of fighting of the PARP blockers well. The combination of a BRCA mutation and PARP blockers is a good example of tailored therapy.”

He continues: “BRCA mutations occur in roughly 20% of women with hereditary breast cancer, but the PARP blockers might be applicable to many more cancer patients. BRCA1 and BRCA2 are proteins which are part of a series of proteins in a biological route. Mutations that can lead to cancer can also occur in the genes that code for these other
proteins. We want to study the workings of these proteins in pieces of the human tumor. If a certain protein does not function properly, then that is a clue that that tumor can probably be tackled with PARP blockers.

**Higher temperature**

Kanaar and his fellow researchers have also discovered that a higher temperature – 42 degrees Celsius (107.6 degrees Fahrenheit) instead of the body temperature of 37 degrees Celsius (98.6 degrees Fahrenheit) – slows the repair of DNA damage. He says: “That might explain why cancer patients who are treated with a combination of chemotherapy or radiation on the one hand and hyperthermia (raised temperature, ed.) on the other have a higher survival rate than without hyperthermia. We have shown that the BRCA2 protein does not function as well at 42 degrees Celsius. We are studying whether applying PARP blockers can further enhance the effects of hyperthermia.”

The researchers have first studied the process in cultivated cancer cells in plastic tubs and then in animal trials. Next, pieces of tumor have been removed from patients to study under raised temperatures in the laboratory. Kanaar: “Now we are going to ask patients whether we can remove a piece of tumor twice: once before the tumor has been heated and once after the tumor location has been heated in a hyperthermia device. In the lab we will study whether heating has slowed the repair process. Once that study has been completed successfully, I see no reason not to continue the study in patients.”
‘Research aimed at individual treatment of patient’
The immune system in patients with mesothelioma (asbestos cancer) does not function properly, allowing the cancerous cells to proliferate. The research team led by professor Joachim Aerts is trying to revitalize the immune system.

“The immune system plays a crucial role in the prevention of cancer,” lung specialist and oncologist professor Joachim Aerts relates. “Unwanted changes are constantly occurring in cells. When everything is functioning properly, these derailed cells are recognized and cleaned up. But cancer occurs when the derailed cells can hide from the immune system or deactivate this system, for example by secreting certain chemicals. The first process will occur in cancer patient A, the second in patient B, and a combination in patient C.”

He continues: “It is important to the treatment to know which process is playing a part. Only then can you offer a therapy tailored specifically to that person: personalized medicine. There is not much point in treating patient A with a medication that slows the production of the chemical which enables the cancerous cell to suppress the immune system. This medication should rather be given to patient B. A lot of attention has been paid to the role of the immune system in the development of cancer over the past years, but in my opinion there is not enough focus on the individual patient. Due to financial considerations the concentration lies on medicines which can be applied to lots of people. Our research is aimed at the individual treatment of patients.”

Aggressive
In mesothelioma, also known as pleural or peritoneal cancer, one large tumor commonly develops on one side of the chest cavity. It is an aggressive type of cancer, but it does not metathesize until very late in the process of the disease.

Aerts: “We think most mesothelioma cells have a special characteristic: they can shield themselves very effectively from the immune system. The cells inside the tumor lack the cells from the immune system which are involved in the cleaning up of cancerous cells. In a smaller patient group there are clean up cells, but they are inactive.”
Poor prognosis

Asbestos cancer is currently incurable. Only one in seven patients is still alive a year after the diagnosis, in spite of extensive treatment.

Asbestos is illegal in the Netherlands. Still there are 500 new patients every year. On the one hand this is because people are getting older: the odds increase that they develop mesothelioma during their life after being exposed to asbestos at some time. On the other hand because asbestos still exists, in buildings for instance, and people are exposed to this.
Dealing with mesothelioma is made even harder by the changing behavior of the tumor. At first the tumor tries to remain invisible to the immune system. Aerts: “The proteins in the wall of the cancerous cells, which can betray that an unwanted intruder is involved, are shielded. After a while, for instance due to a treatment, remaining invisible is no longer sufficient. The tumor then switches to a different system: the production of chemicals which suppress the defensive cells. The type of chemicals produced can change constantly.”

**Attacks**

T cells are the cells of the immune system which can kill the tumor cells. They do this after they have been activated by so-called dendritic cells. These show the T cells the molecules by which they can recognize the tumors. The T cells ‘remember’ the molecule presented and recognize it later in the tumor cells. They then attack the tumor cells. Ten years ago the research group of Aerts and Dr. Joost Hegmans, scientific researcher into pulmonary diseases, began a new approach to mesothelioma cells.

Aerts: “We collected dendritic cells from the blood of the patient and in the lab exposed them to cancer cells which we had also taken from the patient. Then the dendritic cells were re-injected. The method worked: the T cells of these patients became active again. Based on this study it is impossible to say whether the life expectancy of the patients was lengthened. You would have to do a comparative study with a group of patients which does not receive the treatment. One important downside to the approach was that it proved difficult to collect enough cancer cells from the patient.”

The method was adapted. Aerts: “We developed mesothelioma cell lines. These are cells that are kept alive in the laboratory in special bottles. They can be easily cultivated until there is enough material to expose the dendritic cells of the patient to. We use a collection of cell lines. Each cell line stands for a certain type of mesothelioma. This increases the chance of effectively dealing with the tumor, because the dendritic cells have been confronted by several types of tumor cells. The dendritic cells are then injected into the patient. Then the dendritic cells get to work: they activate the T cells and these go hunting for the tumor.”

Thanks to the new method the researchers always have enough material to expose the dendritic cells to. Aerts warns against high expectations: “We first have to study whether the current combination of cell lines is the ideal one. We don’t know for example whether this composition will be effective on all patients. This approach will also not work if the tumor has developed a mechanism to stop the T cells from recognizing the tumor. But then we can start looking into combination treatments.”
‘Preparing to attack’

“The liver is a tolerant organ. Sometimes so tolerant that liver cancer is given a chance,” says gastroenterologist Dave Sprengers. His research team is trying to restore the imbalance in the immune system.

‘In liver cancer the cells of the immune system do not work together properly’
Sprengers: “Everything we eat, everything that is absorbed from our intestines, passes through the liver. It would not be useful for the immune system of the liver to react intensely to all these chemicals which are foreign to the body. But sometimes this tolerance goes too far: divergent cells are not recognized as such. That’s when liver cancer has the chance to develop. It is not surprising that the liver is the organ most affected by the metathesizing of other cancers (such as skin cancer, intestinal cancer or cancer of the kidneys).”

**Invaders**

Cell types involved in the immunoreaction to invaders circulate all through the body, including in the liver. Among other types, T cells, regulatory T cells and dendritic cells turn on bacteria, viruses and tumor cells. The dendritic cells present small pieces of the tumor cells to the T cells, so that these recognize the tumor and attack it. The regulatory T cells ensure that that process is not too intense. They step on the brakes.

“In liver cancer the cells of the immune system do not work together properly,” says Sprengers. “T cells around or in a liver tumor are inactive. They appear to be numb. At the same time the immunosuppressive regulatory T cells are present in large numbers. So it appears that the balance between the active and the suppressing immune cells is disturbed. The tumor cells themselves appear to play a part in this process: they communicate with the T cells through receptors or through chemicals they produce. This suppresses the T cells. In this way they work together with the regulatory T cells to suppress the immunoreaction which is supposed to clear up the tumor.”

**Activating and suppressing**

The research team led by Sprengers is attempting to restore the imbalance in the immune system. “We are searching for ways to influence the immunological environment in such a way, that the cancer is tackled. On the one hand we are trying to reactivate the T cells which are supposed to recognize the cancer cells. On the other hand we are trying to weaken the regulatory T cells which are suppressing the immune reaction. To achieve this we are using drugs which are already being applied to other forms of cancer, like melanoma (an aggressive type of skin cancer, ed.). We are still at the stage of laboratory research.”

The Rotterdam approach is unique, Sprengers states. “We are using the patient’s own tumor material and not cell lines or animal models like most other researchers. The tumor is removed during surgery. With patient consent a part of this tumor is then used in our research. We also take blood, so that we can compare the results of the liver cells with those of the blood cells. The tumor material is ‘mashed up’ into loose proteins which are presented to the T cells from the tumor material and from the blood. We then study the effects of those proteins on the activity of the T cells.”

**Restore**

Sprengers hopes that in the future it will become possible to activate the T cells of the patient using medication, and to suppress the regulatory T cells. That should restore the imbalance.

“But before we reach that stage, we have to first unravel how the immune system is disturbed in liver cancer and how we can correct this,” he says. “Collaboration within Erasmus MC is vitally important. We confer with other groups that are working with immunotherapy in other types of cancer. The group of professor Joachim Aerts for example, which is studying mesothelioma (asbestos cancer, ed.) (see page 74). We are joining forces to find the ultimate therapy.”
Predictive bacteria

If you can predict with a certainty of close to 100% that a woman will not become pregnant after an IVF-treatment, you can treat her more effectively, save costs and prevent disappointment. Urology researcher Dr. Dik kok: “We are developing a test that can be used in IVF-clinics around the world.”

Scientists always assumed that the bladder is sterile. But Kok - and other research groups within the country and abroad - refuted this dogma by examining urine in a new manner. He says: “It is true that with a normal culture you don’t find any bacteria, but DNA-analysis sometimes shows a complete collection of all these bacteria, otherwise known as a microbiome.”

Surviving
After this discovery Kok was curious what happens to the microbiome when the physical situation changes, for instance during pregnancy. His explanation: “Bacteria will do anything to survive.”

He and his PhD-student Delshad Maghdid approached professor Joop Laven and Dr. Nicole Beckers of the sub department of Reproductive Medicine at Erasmus MC. Their proposition: conduct a study among women who want to undergo IVF-treatment. Kok: “Prior to that treatment we collected their urine and again thirty weeks later. On average this was sixteen to eighteen weeks after the embryo had been implanted. Eventually there were two groups: the one group did get pregnant, the other did not.”

Reversed
Analysis of the urine samples showed that the urine of women who did become pregnant contained many Lactobacilli and few Staphylococci before the IVF, but this was reversed after a successful IVF attempt. The

urine of women who did not turn out to be pregnant contained many Staphylococci and few Lactobacilli both before and after the IVF.

Kok: “Based on those urine samples I began to predict which women would not get pregnant. It turned out that the changes in the population of bacteria were excellent predictors for the success of the IVF. If I also take the presence of other types of bacteria into consideration in my analysis, the prediction is nearly 100% accurate.”

Starvation
According to the researcher it is not the bacteria themselves which influence the chances of successful IVF-treatment. After all, they are in the mucous membrane of the urinary tract, while the embryo is in the endometrium.

Kok: “We think that the bacteria register the chances of survival of the embryo in the mucous membrane of their host. The combination of bacteria that we have found turns out to prefer the same circumstances that the embryo needs to survive when placed in the womb during IVF. In other words: when the woman does not have the correct mucous membrane, both the bacteria and the embryo die of starvation.”

The Netherlands Genomics Initiative has granted a subsidy of a quarter of a million euro for further research.
Modern medicine is predictive, preventive, personalized and participatory. Its focus is shifting from disease to wellness. Erasmus MC professionals apply this novel approach in scientific research and in everyday patient care.

While science and technology are rapidly creating possibilities for targeted prevention and treatment, healthcare is also changing by an increasing participation of patients.

**Cancer**
The field of oncology has a frontrunner position in personalizing medicine. Technological advances have paved the way for a precision treatment tailored to both patient and tumor. Professor Roland Kanaar is convinced that DNA is the key to targeted anti-cancer therapies. “We want to use our knowledge to prevent people from going into treatments they won’t respond to,” he says.

**Obesity**
Erasmus MC’s Center for Healthy Weight also applies a personalized approach. Founders of the Center Dr Liesbeth van Rossum and Dr Erica van den Akker explain: “Obesity is a complex condition, which means that standard treatment is only effective for a small group of patients. Each patient is different and this calls for tailored treatment.”

**Women’s health**
Diseases manifest in different ways in men and women. Research in this area will lead to better targeted treatment strategies than a ‘one size fits all’ approach. This is particularly clear in the field of cardiovascular medicine, where misdiagnosis frequently occurs because people are unaware of gender differences. “This can result in a delayed treatment,” explains women’s health expert Dr Maryam Kavousi.

**Value-based care**
In modern medicine, patients have a voice in the complete ‘customer journey’ from making an appointment to co-decision making about treatment options. The clinical question ‘what is the matter?’ is being rephrased as ‘what matters to you?’ Dr Jan Hazelzet: “We want our patients’ wellness to be our first priority. This starts with the values that we should promote. That is professional behavior.”

**Conference**
Erasmus MC is the initiator of the 2nd Transatlantic Conference on Personalized Medicine, to be held in Rotterdam on 8 and 9 October 2015. The conference connects science, society, healthcare, industry and policy to bring personalized medicine solutions into clinical practice.
JOIN US IN ALIGNING P4 MEDICINE: PERSONALIZED, PREVENTIVE, PREDICTIVE, PARTICIPATORY

While science and technology are rapidly introducing new possibilities, major changes are set in motion by an increasing participation of patients and consumers. The Transatlantic Conference on Personalized Medicine (TCPM2015) will bring together opinion leaders and decision makers from science, society, health care, policy and industry with the aim of creating transatlantic and European platforms and pathways for introducing applications of personalized medicine in prevention, cure and care.

TCPM2015 focuses on knowledge valorization and consortium building within the international science policy frameworks. Themes include: 'Diabetes'; Value Based Health Care; Cardiovascular & Women's Health, Public Private Partnerships; Global perspective in PMed.

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Caroline Klaver, Professor of Epidemiology and genetics of eye diseases

Vici and ERC Consolidator Grant recipient,
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