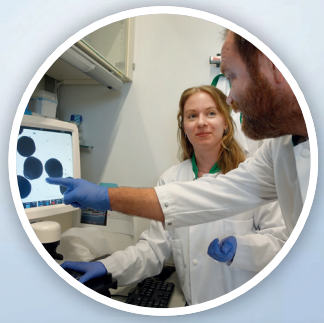
Leiden University Medical Center

REGMED READS

A MAGAZINE ABOUT REGENERATIVE MEDICINE AT LUMC



IN THE LABORATORY

TOWARDS THE CLINIC

CONNECTING AND INSPIRING

Tomorrow's medicine, today at LUMC

LUMC RegMed

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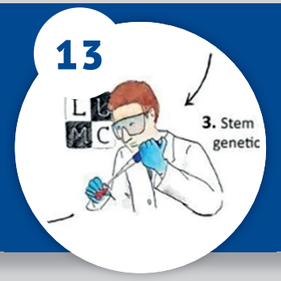
Towards the clinic



In the laboratory

Connecting and inspiring

Colophon

Edited by
- Mandy Segers, project manager regenerative medicine
- Hessel Honkoop, advisor science communication regenerative medicine

In collaboration with the Directorate Communication
- Sylvia Bouwmeester
- Annemarie Schrijen-Zwaanenburg
- Lennart 't Hart

Contributions by
- Giorgia Mazzini, PhD Student department of Molecular Epidemiology
- Lieke van Kempen, PhD Student department of Medical Ethics and Health Law

Design
- Engelen & de Vrind

Photography
- Niels Busch, commissioned by reNEW
- Marc de Haan
- Editorial board

Medical illustrations
- Manon Zuurmond

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LUMC
Albinusdreef 2
2300 RC Leiden
www.lumc.nl

Disclaimer
www.lumc.nl/disclaimer

Contact
regmedtheme@lumc.nl

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PREFACE

Dear reader,

In front of you is the very first edition of *RegMed Reads*. Thé magazine dedicated to regenerative medicine at Leiden University Medical Center (LUMC).

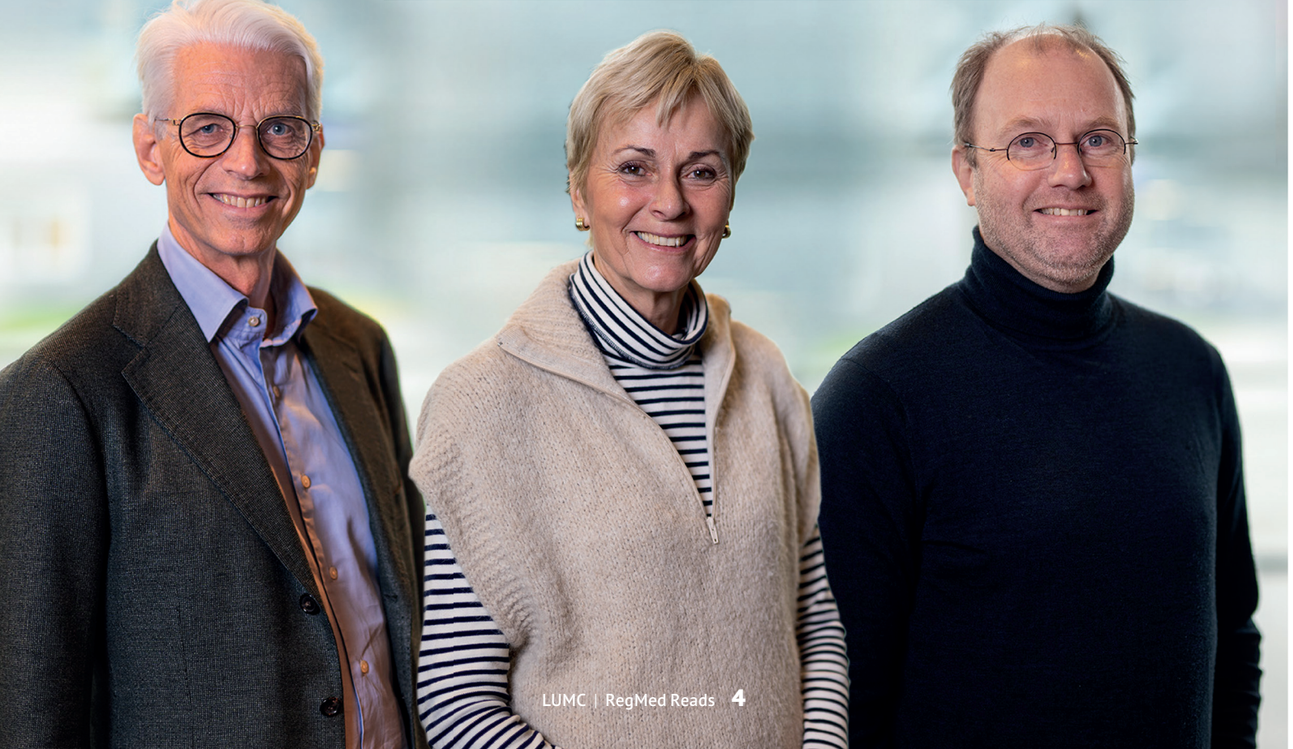
Regenerative medicine holds a prominent position within LUMC and is one of the three societal outreach areas of the hospital. Across our entire academic medical center, we are working on tomorrow's medicine.

In this magazine, you will read about some of these exciting developments. It is an exhilarating time, as years of investment in research are now paying off. New regenerative treatments developed at LUMC are reaching our patients. For example, you will read about traveling cells that cure congenital immune disorders, or the use of reprogrammed stem cells following kidney transplants – a European first.

This edition also pays special attention to collaboration with other companies and knowledge institutions in Leiden. Learn about the Leiden Bio Science Park, the largest Life Science campus in the Netherlands. And about our partnership with Leiden University in educating a new generation of professionals. These partners are indispensable for the development of new regenerative therapies at LUMC.

On behalf of the editorial team, we wish you an enjoyable read!

Prof. dr. Ton Rabelink, prof. dr. Christine Mummery and prof. dr. Niels Geijsen
Regenerative Medicine of Tissues and Organs – LUMC Theme for Innovation



What is regenerative medicine?

Regenerative medicine is a new way of treating that helps sick cells, tissues, and organs work properly again. We do this by repairing, replacing, or restoring cells, tissues, and organs after damage caused by disease or injury.

In a society where more and more people are aging, chronic diseases put great pressure on both society and patients themselves. As people age, the health of their tissues and organs deteriorates. In some individuals, this happens more rapidly due to diseases such as heart conditions, kidney problems, or diabetes. Regenerative medicine offers hope that these patients can be truly cured.

How does it work?
Many of our researchers work with special cells, called stem cells. These cells can divide infinitely in the laboratory and develop into different types of cells, such as heart muscle cells or skin cells. This allows us to grow new cells or even small organs in the lab.

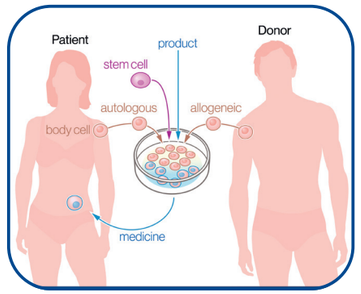
We can transplant these cells directly to cure diseases (cell therapy). And, with new techniques, we can also first repair them inside or outside our body (gene therapy). Finally, we can study them to better understand diseases and develop new treatments (disease models). It may sound unbelievable, but in this magazine, you'll find examples of how researchers at LUMC explore these avenues for a new generation of therapies!

What is the impact?
Regenerative medicine is an innovative and socially relevant field, with potentially a very large impact. That's why it's one of the societal outreach areas of LUMC. The field helps people age healthily and can contribute to manageable healthcare costs. With large-scale application, our healthcare system will change: patients no longer need to take medication for the rest of their lives but can be cured with their own cells, gene therapy, or repaired tissue in a single treatment.

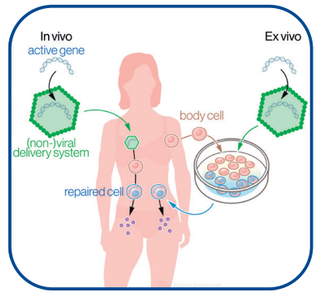
This requires new laws and regulations because current rules don't align with these developments. There are also questions about costs, access to these often expensive treatments, and ethical issues. Therefore, collaboration with health insurers, patients, and society is essential.

If we approach this properly, regenerative medicine can bring about economic growth and a healthier society. For this, we need people with the right knowledge and skills. The students we train at LUMC are therefore crucial for the future.
We are proud of all the researchers, doctors, and entrepreneurs who are part of the ecosystem that makes all these innovations possible. ■

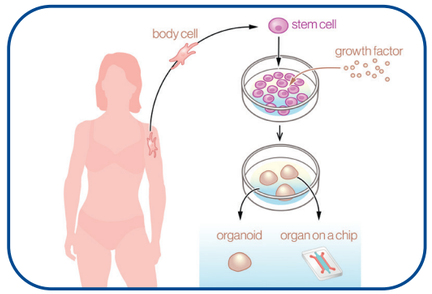
Cell therapy



Gene therapy



Disease modelling



LUMC first in Europe to provide reprogrammed stem cells to patients receiving a kidney transplant

LUMC is the first hospital in Europe to administer a therapy based on reprogrammed stem cells to a patient with a donor kidney. This administration is part of a clinical study assessing the safety of this innovative therapy. In a later phase of the research, it will be examined whether the treatment helps prevent rejection of the donor kidney.

In 2006, Japanese researcher professor Shinya Yamanaka revolutionized the world of stem cell research. He discovered a way to transform ordinary body cells (such as skin and blood cells) into stem cells. These reprogrammed stem cells, also known as induced pluripotent stem cells (iPSCs), can change into any cell type in the human body without the need for embryonic material. Due to this ability, iPSCs are widely used to study diseases in the lab and test medications.

A first in Europe

For the new cell therapy at LUMC, iPSCs have also been used. The use of these cells for patient treatment is exceptional and still very rare. “This is the first time in Europe that a therapy derived from iPSCs has been used in patients with a transplanted kidney. It is truly unique,” says dr. Siebe Spijker, nephrologist at LUMC and head of the trial.

Preventing rejection with bags of cells

With a few modifications, the iPSCs are converted into mesenchymal cells (MSCs). Six and seven weeks after the kidney transplant, these cells – approximately 100 million at a time – are administered to the recipient via an infusion. “The MSCs instruct the immune system not to attack the new donor kidney so aggressively. The idea is that, thanks to the cells, patients will need less rejection medication to maintain the kidney. These medications have many side effects,” explains Spijker.

LUMC has previously conducted successful trials using MSCs obtained through a bone marrow puncture. A challenging procedure for the donor, from which only one patient can be helped. Thanks to the new therapy, this could become a thing of the past. “With iPSCs, you can create an unlimited number of MSCs in the lab and help many more patients. This offers many possibilities,” says Spijker.

A new kidney from skin cells?

According to Spijker, the cell therapy is a “great first step” for future stem cell treatments at LUMC. “iPSCs have a lot of potential. For example, we are already creating mini-kidneys or insulin-producing cells from them in the lab. In the future, we may be able to create transplantable kidneys and other organs from iPSCs.”

How long it will take to generate functional kidneys from iPSCs is difficult to say, according to Spijker. “But my goal is to make it possible during my career,” says the 40-year-old nephrologist.

Want to learn more?

Spijker discusses the research on NPO Radio 1 (in Dutch)! ■

LUMC facilities: a nursery for regenerative innovations

The research facilities at LUMC provide researchers with the opportunity to utilize a wide range of state-of-the-art equipment and knowledge for research and development within regenerative medicine. In this way, they truly serve as a nursery for regenerative innovations. Here, you can read about two of these facilities.

The Center for Cell and Gene Therapy

The Center for Cell and Gene Therapy (CCG) at LUMC is a leading production and development facility for advanced therapies, such as cell and gene therapies. To ensure the safe and high-quality development and production of these medicines, strict guidelines must be followed, known as Good Manufacturing Practice (GMP).

The CCG is one of three GMP facilities within LUMC and plays a crucial role in translating innovative therapies into clinical applications. Researchers aiming to bring a new therapy to patients can turn to the CCG. The center helps them refine their production process to meet high-quality standards, ensuring the medicine is suitable for patient use.

The CCG houses six cleanrooms, where medicines are produced safely in a sterile and controlled environment. Over its 25-year history, the CCG has developed and delivered numerous cell and gene therapies to patients. These include immune cells targeting malignancies, such as CAR-T cells, as well as genetically modified stem cells for treating children with immune deficiencies (p.13) and pluripotent stem cells (p.22) for the production of more regenerative therapies.

As a vital link in the innovation of advanced medical treatments, the CCG contributes to the ongoing development of personalized and regenerative medicine within LUMC.

Leiden hiPSC Center

The Leiden hiPSC Center, located in Mirai House at the LBSP, is part of the LUMC and has years of experience in generating and modifying human induced pluripotent stem cells (hiPSCs) for research. These versatile cells are widely used to study development, for disease modeling, drug testing and the development of cellular therapies. The facility offers a range of services to researchers.

The Center offers multiple well-characterized stem cell lines from ‘healthy’ donors for research. Additionally, it supports researchers in generating patient-specific hiPSCs from primary tissues such as blood, urine, or skin. The Center has the capacity to generate about 40 hiPSC lines per year and a total of 370 hiPSC lines have been generated until now.

The facility also specializes in genetic modification of hiPSCs with CRISPR/Cas9, for example in order to repair small scale mutations in patient-derived hiPSCs resulting in (isogenic) control lines. But also for generating knock-out or reporter hiPSCs. In addition a set of control hiPSCs equipped with an acceptor site in safe harbour loci such as AAVS1 or CLYBL facilitating the efficient integration of large DNA payloads is available.

Beyond these services, the Center shares its expertise with stem cell researchers who need support with their projects. Being a consortium member of reNEW, RegMedXB, NOCI, and hDMT-INFRA, it maintains strong connections with scientists worldwide. To make hiPSCs widely accessible, the Center regularly organizes hands-on training courses for researchers within and beyond these networks. ■

Heiko Locher (m) in a meeting with his research group.

“I can combine my curiosity with the human aspect.”

As an ENT specialist, dr. Heiko Locher sees patients with hearing and balance disorders – conditions caused by problems with the inner ear – on a daily basis. Determined to offer these patients new treatment options, he combines his work as a physician with research in regenerative medicine.

You work as an ENT specialist at LUMC. What kinds of conditions do you encounter?
As a doctor and surgeon in the ENT department, I deal with a variety of hearing and balance disorders, ranging from sudden or congenital deafness to Ménière’s disease. Working in a hospital makes you acutely aware of what you can and cannot do for patients with these conditions.

Hearing aids and cochlear implants allow us to help many patients, but for others, we have little to no solutions. New treatments are truly needed for these patients. That’s what my colleagues and I are working on within regenerative medicine. I combine my work as a physician and surgeon with scientific research.

> *Research itself gives me a lot of energy, but being a doctor in daily contact with patients adds even more motivation – for me and for those around me.*

Why did you choose to combine medicine with research?
My interest in research goes way back to my medical studies at ErasmusMC in Rotterdam. During a neurology course, I was introduced to a different way of thinking: Where do symptoms come from? How does it work? And why does it go wrong? I wanted to explore that further, so before starting my clinical rotations, I pursued a research master’s in neuroscience. I loved it.

In the lab, I also – whether by chance or not – had my first real encounter with the inner ear. My fascination with this organ has never faded. Now, I see patients, perform surgeries, and lead a research group. It’s a busy combination, but I like it a lot. I can merge my curiosity with the human aspect of medicine.

What is the focus of your research?
There are very few treatment options for our patients, largely because so much is still unknown about the causes of various inner ear disorders. In our lab, we aim to change that – so that our findings can serve as the foundation for new therapies.

All our research is conducted on human tissues and cells. Since I perform surgeries, we sometimes have access to rare inner ear tissue from my patients, providing valuable insights. Additionally, we grow so-called inner ear organoids from stem cells – small 3D models of the organ that we cultivate in the lab.

With these organoids, we can simulate inner ear damage caused by different factors. For example, we study the effects of chemotherapy on inner ear organoids, as well as the impact of cytomegalovirus – the leading cause of congenital deafness. Lastly, a major part of our research focuses on genetic hearing disorders caused by DNA mutations.

How does this research work?
To study genetic hearing disorders, we create organoids with the same DNA mutation as our patients and compare them to healthy organoids. This allows us to see how the mutation affects inner ear cells and develop therapies to precisely correct the defect. Instead of directly altering DNA, we target RNA, which transmits genetic instructions to the cell’s protein-making machinery.

Right now, we are primarily focusing on patients who gradually lose their hearing later in life. They are easier to treat than those who suddenly become deaf or are born deaf. The idea is that, in the future, all our patients will undergo a DNA test first. This will help determine whether their hearing loss is caused by a genetic mutation – even in adults. If so, they may be eligible for new targeted therapies. If we intervene early, we can prevent further hearing loss and reduce reliance on hearing aids – or even prevent complete deafness. That would be a real game-changer!

How does your perspective as an ENT specialist benefit your research?
Research itself gives me a lot of energy, but being a doctor in daily contact with patients adds even more motivation – for me and for those around me. It also directly benefits our research. It shapes our decisions: Which research directions do we pursue? What can we do to maximize the chances of clinical application? Because I work as a physician, I have a much better understanding of the potential impact of our research on patients compared to someone who isn’t in the clinic.

I’m 42 now, so I still have a good number of working years ahead. Looking at recent advances in regenerative medicine, I am convinced that some therapies currently in the lab will make it to the clinic within my career. How amazing would it be if some of those treatments come from our own lab! ■

Leiden: where history and regenerative medicine meet

Leiden University runs the interdisciplinary program Regenerative Medicine. As part of this, an innovative educational project has started in 2023: what if we bring together students from History and Biomedical Sciences? Students from both fields worked together to write a story that combines the past and the future through the lens of a historical object. Teachers from the Faculty of Humanities and LUMC guided them, in collaboration with the Rijksmuseum Boerhaave and the online platform *Things That Talk*.

In 2024, Biomedical Sciences students Caitlin, Mieke, and Megan, along with history students Noa and Rosalie, delivered the best presentation. We asked them about their experiences.

What was the first thing you thought when you heard about this project?

Rosalie: "I actually missed this project when I chose the *Equalizers* course in my History master's, so it kind of came out of nowhere. When I suddenly got enrolled in the *Stem Cells, Regeneration, and Development* course, I thought, 'What's going on?' I didn't quite imagine how dusty history and hard science would complement each other."

Megan: "I read that the course was about regenerative medicine, so I thought, 'I'll take that.' But I didn't expect we would get this assignment. At first, I didn't think it fit with regenerative medicine at all. I wondered, why are we doing this?"

Mieke: "There were other students who didn't choose the course because of this project, but I thought: it's just one week out of four."

Caitlin: "I actually found the interdisciplinary collaboration in this project interesting, which is why I chose the course. I'm really passionate about science communication, so I thought, 'Wow, this is a cool way to approach it.' And visiting the Rijksmuseum Boerhaave was especially fun for me."

So most of you were quite skeptical about the project. Did this scepsis eventually turn to enthusiasm?

Megan: "In hindsight, I quite enjoyed it. I actually dropped history as soon as I could in high school. But I ended up enjoying exploring that side of things a bit. I found the part written by the history students really interesting."

> *"I didn't quite imagine how dusty history and hard science would complement each other."*
> ROSALIE

Rosalie: "My experience was also really positive. From the start, it was actually fun, which helped a lot. The fact that the hard science, which I usually run away from, actually goes quite well with history really surprised me. It was nice to see that we could really help each other in that sense. The collaboration aspect really surprised me."

Caitlin: "Our guide from Things That Talk, Fresco, said at one point that he could almost no longer distinguish between who the Biomedical Sciences students and who the History students were. I felt the same way while we were collaborating. When we were brainstorming about how things might have gone or what effects it could have had, it didn't really feel bound to a specific science anymore. That was really cool to see."

What will you take away from this project for your future career?

Megan: "Thinking more outside the box. I think that's something I'll take with me in my future work. And also making it into a fun story. I think what we often do is just stick to the facts and forget to tell the story."

Mieke: "I used to see creativity as something that doesn't really go with objective facts. But we actually did that here, which I thought was really cool. I think that's something valuable to take with me. Because we will often be working with objective facts, things we measure and know. But now we've learned that you can still add a creative aspect to that."

Rosalie: "I have to say, I agree with the others about the creativity. I've always had a tendency to stick strictly to the facts and not really go beyond that. Maybe it's a bit of a shame that I never did that, especially in a subject like history, where you can do that a bit more."

Caitlin: "Because you can think about it so creatively, you can use many more ways to engage the reader. That's really cool. I think you learn tricks this way. Like appealing to emotions, for example. It obviously looks very different in a scientific article, but I think those are things you can practice.
And especially in science communication to a wider audience, I think these are really useful things to work on. You can keep people interested by focusing less on the dry facts."

What would you like to say to future students who are unsure about joining this project?

Mieke: "It was probably the most fun week out of the four. And I'm someone who is not at all into history or ethics. I would say: definitely give it a chance. And if you don't like it after all, you've still gained new insights."

About the Object

The object chosen by the students is a practice doll for obstetrics, made between 1790-1820. The doll was used at the Academic Hospital Leiden (which later became LUMC) to train male students in obstetrics. ■

Want to know more about this project and how teachers experienced it (only in Dutch)?

LUMC and LBSP: a shared focus, a strong engine for innovation

LUMC is proud to be part of the largest Life Sciences and Health campus in the Netherlands: the Leiden Bio Science Park (LBSP). In 1984, LUMC was one of the six founding institutions of this park. Since then, the LBSP has grown significantly, now bringing together more than 500 organizations that collaborate on the "Future of Health".

LUMC and LBSP share the same goals and priorities, particularly in the field of regenerative medicine. This shared focus makes us a strong engine for innovation.

We are proud and pleased that the LUMC is an integral part of our vibrant and innovative ecosystem, where numerous high-quality Life Sciences and Health applications are developed and produced. Science, education, healthcare, entrepreneurs, and government come together here to drive innovation and translate advanced knowledge into treatments for patients.

ESTHER PETERS, DIRECTOR LEIDEN BIO SCIENCE PARK

From knowledge to society – valorization

Valorization means sharing knowledge from research or using it to create something that benefits society. Often, LUMC develops technologies or products that can be brought to market to improve research or directly help patients. Researchers can apply for patents, collaborate with companies, or even start their own businesses.

The many companies and start-up opportunities at LBSP make it an ideal environment for valorization of knowledge that springs from the hospital. The park provides access to knowledge, talent, a vast network, and investment opportunities, making it an attractive hub for both growing and new businesses. Various companies, such as Ncardia, NTrans Technologies, Genewity, NecstGen, and StemX Bio, are contributing to innovation in regenerative medicine.

"At NecstGen, we enable the next generation of therapies by supporting the development and GMP production of cell and gene therapies. In doing so, we help bridge the gap from research to the clinic, ultimately making a difference in patients' lives." – Paul Bilars, CEO, NecstGen

Sharing knowledge has always been an essential part of valorization, especially in an innovative field like regenerative medicine. That's why we actively participate in activities at and organized by the LBSP, such as visits from international delegations and TechTalks. During these events, researchers share their latest developments with other professionals, fostering mutual learning and potential new collaborations. We also take part in the Dutch Bio Science Week (formerly LSH Week), which includes public events like the Public Regeneration Day and the Leyden Academy Vitality Walk.

Education: the future of regenerative medicine

For years, LUMC has been training students to become top scientists and medical professionals. Regenerative medicine is a rapidly growing field with a significant impact on society. To ensure our education keeps pace with developments and meets the needs of the sector, we focus on preparing future professionals who can truly make a difference.

Students can complete internships at the university as well as at companies within the LBSP. We also collaborate on new educational initiatives to ensure students are well-prepared for practical applications. One example is a course jointly developed by the Biomedical Sciences (LUMC) and Bio-Pharmaceutical Sciences (Faculty of Science) master's programs in collaboration with the Biotech Training Facility (BTF). In this course, students gain a deeper understanding of regenerative therapy development process through a combination of theoretical and hands-on training. Through our shared focus, LUMC and LBSP together contribute to innovations that have the potential to change lives. ■

TechTalk

LEIDEN BIO SCIENCE PARK

More info

Traveling cells cure congenital immune disorders

Researchers from the Department of Immunology at LUMC have developed a groundbreaking therapy to cure patients with the congenital immune disorder RAG1-SCID. This therapy is the first of its kind for this specific SCID variant. It utilizes stem cells from the patient's own bone marrow, which are repaired in the lab. The first five patients have already received these corrected cells. "With our treatment, the cells travel – not the patient."

Bubble boy disease

SCID (Severe Combined Immunodeficiency) is a rare and severe congenital disorder in which the immune system fails due to a genetic mutation. SCID patients are unable to protect themselves from infections, making even a common cold potentially life-threatening. In the past, these patients were kept alive in sterile environments, such as plastic bubbles – leading to the nickname "bubble boy disease."

Traveling cells as an alternative

SCID patients currently rely on finding a suitable donor for a bone marrow transplant. "This treatment is far from ideal," explains professor Frank Staal, group leader at LUMC. "Even if a donor is found, one in four patients does not survive. An even larger group experiences severe side effects from the transplant, which can significantly impact their quality of life."

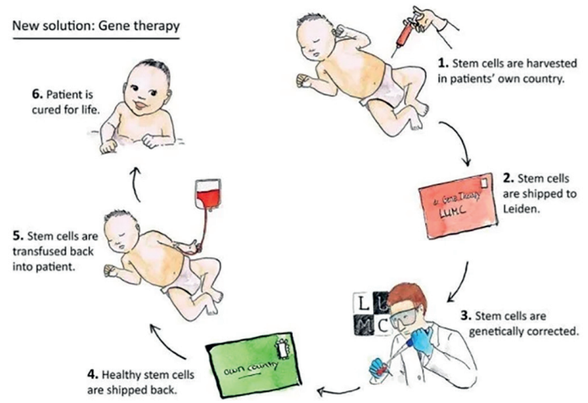
Now, researchers have developed a unique alternative. Stem cells are extracted from the patient's own bone marrow and sent to LUMC's Center for Cell and Gene Therapy (p.7). There, the cells are cultivated, and the genetic defect is 'repaired' using gene therapy. Staal explains: "We are currently correcting mutations in the RAG1 gene, which prevents patients from producing T- and B-immune cells. In the future, we aim to apply this therapy to other genes, such as RAG2." The repaired cells are then frozen and sent back to the patient. Through an infusion, the patient receives their own corrected cells, which settle in the bone marrow and start producing functional immune cells.

Around the world

The first five patients in the clinical trial have now been treated – two from the Netherlands and one each from Turkey, Poland, and Germany. They are showing promising initial immune recovery and are being monitored to assess long-term safety and effectiveness. With all signs pointing to success, the same approach could soon be used to treat patients as far away as Australia.

The patients from Poland and Turkey were treated according to the "ideal model" and never even traveled to Leiden themselves – only their cells made the journey to LUMC and back. "This process has been done before with donor stem cells, but never with a patient's own corrected stem cells," explains pediatrician dr. Lisa Ott de Bruin. She concludes: "By correcting the patient's own cells, we eliminate the risks associated with donor bone marrow transplantation." ■

New solution: Gene therapy



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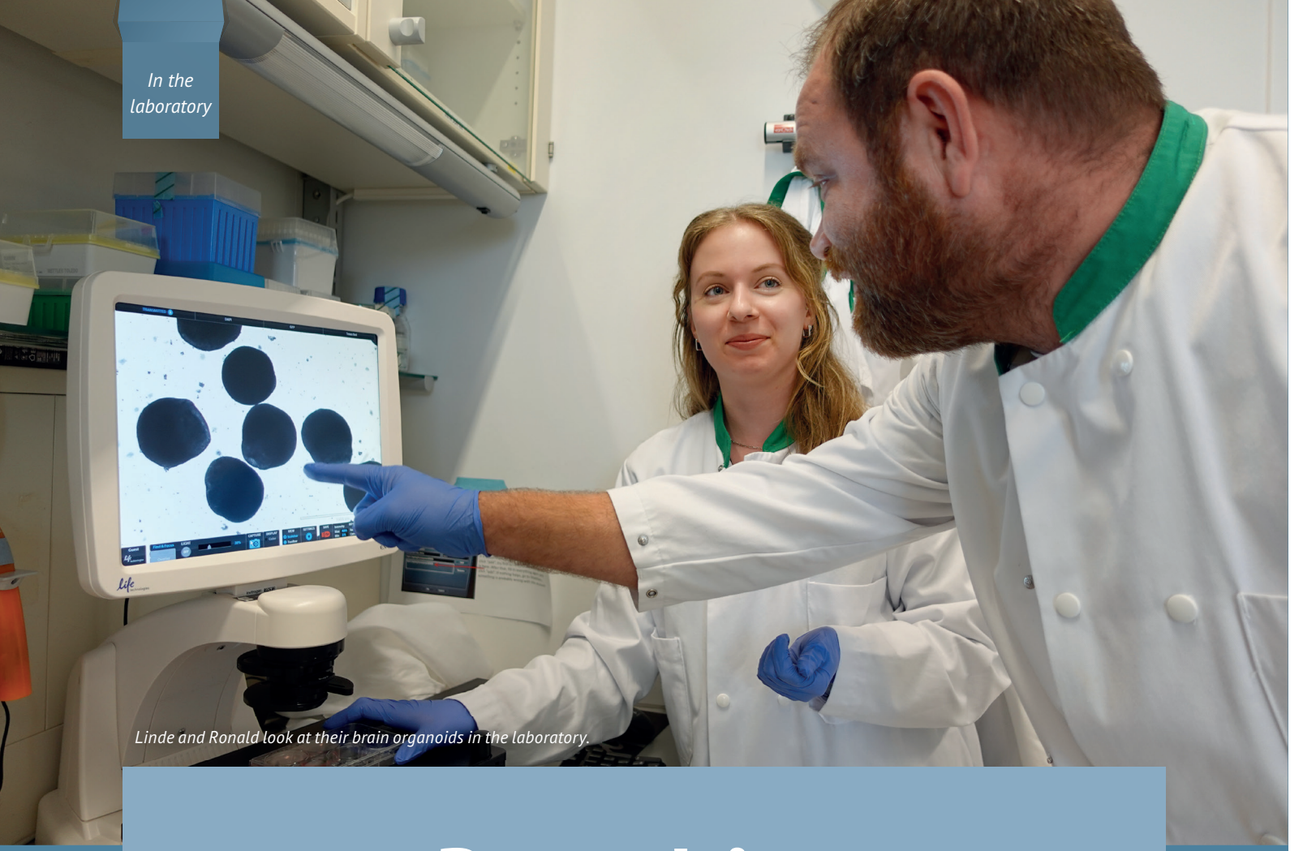


In the laboratory

Linde and Ronald look at their brain organoids in the laboratory.

Research into new treatments for brain diseases

At LUMC, researchers are investigating new treatments for hereditary, often rare brain disorders. This research is conducted using tiny 3D models of the human brain, known as organoids. Researchers Ronald Buijsen and Linde Bouwman from the Department of Human Genetics share insights into their work.

Brains in decline

Ronald: "Linde and I are part of the NeuroD research group, led by Professor Willeke van Roon-Mom. We study hereditary brain diseases, specifically neurodegenerative disorders. In these conditions, the brains of affected individuals gradually deteriorate as nerve cells responsible for controlling the body die off. This happens in diseases like Huntington's disease or spinocerebellar ataxia. We aim to understand what goes wrong in these patients and find ways to treat these diseases."

Linde: "To answer these questions, we focus on two aspects. On one hand, we try to recreate these brain diseases in the lab to better understand their development and progression. On the other hand, we develop and test new therapies in the hope of helping patients with these rare disorders in the future."

A brain in a dish

Linde: "To replicate the brain in the lab, we use human stem cells. These can be directed to develop into various types of brain cells. We then combine them to create 3D models of the brain – small spheres with a maximum size of 1 cm, about 1000 times smaller than a real human brain. These are called organoids."

Ronald: "Organoids contain the same structures and cell types as real brains but lack the organization of a fully functioning brain. So, they can't think the way we do!"

Linde: "Exactly! But they do allow us to study brain diseases in a human context without using animal models."

WhatsApp groups

Ronald: "With organoids, we try to mimic key characteristics of brain diseases. For example, nerve cells in our brain communicate with each other, much like being in a WhatsApp group. In patients with brain disorders, these conversations are disrupted – the group might be smaller, or there might be less chatting going on."

Linde: "By comparing diseased and healthy organoids, we learn how these conversations differ and how the disease progresses. This also helps us identify the underlying cause, so we can intervene."

Shoot the messenger

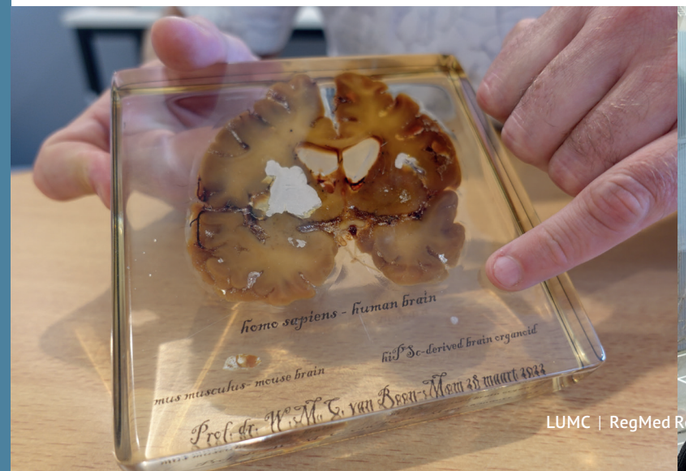
Linde: "Many of the diseases we study are caused by the accumulation of 'faulty' proteins in nerve cells. These proteins contain repetitive sequences in their structure that shouldn't be there. To prevent this, we are developing therapies that correct the instructions for making these proteins – the RNA."

Ronald: "These therapies, called AONs (antisense oligonucleotides), ensure that these harmful repeats don't end up in the proteins. This helps prevent the buildup of faulty proteins and protects nerve cells. We can directly test these AONs on our diseased organoids to see if they work! It all comes together in this approach."

Moving forward together

Ronald: "In our lab, we take the first steps in developing these therapies. Then, we collaborate with companies. The first AON developed in part at LUMC is now being tested for safety in a phase 1/2 clinical trial. We are conducting this trial together with VICO Therapeutics, a company based at the Leiden Bio Science Park."

Linde: "The diseases we work on are severe but also very rare, affecting only 1 to 10 in every 100,000 people. For these patients, it's crucial that research is being done. They are highly involved in our work, as are the physicians treating them. That is incredibly valuable. Together, we will make progress!" ■



In the laboratory

Visiting Mirai House

In 2023, LUMC opened a new location: Mirai House, located at Sylviusweg 62, right in the heart of the Leiden Bio Science Park. More than 120 people from four different departments work together under one roof. Their shared focus on organ-on-a-chip and stem cell research makes Mirai House one of the largest stem cell research centers in Europe. Bas Brinkhof and Marten Engelse proudly manage this LUMC facility.

Take a look inside Mirai House!

1 LUMC shares Mirai House with two other organizations: Astellas and NecstGen. The researchers at NecstGen are our direct neighbors and are located on the same side of the building as LUMC.

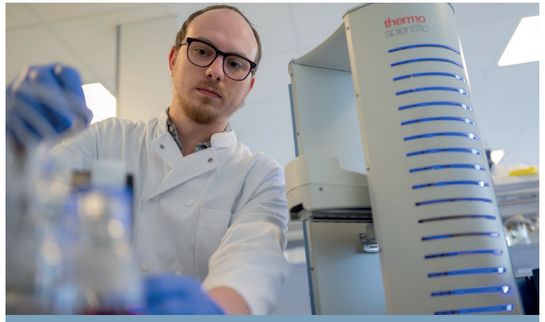
2 On the first floor, you'll find office and meeting spaces. However, researchers spend most of their time in the labs on the second floor. What makes Mirai House unique is that its laboratories are organized by technology rather than by research group. This setup fosters collaboration and enables researchers from different teams to learn from one another.

As mentioned earlier, the work at Mirai House primarily revolves around stem cells. To cultivate these cells, the facility houses multiple large cell culture laboratories. Here, researchers grow stem cells, which can then differentiate into various organ-specific cells, such as those of the heart, skin, kidneys, lungs, pancreas, and inner ear. These differentiated cells are used to study diseases affecting these organs, test new drugs, or even develop new therapies.

3 One of the most important facilities for regenerative medicine research is also housed in Mirai House: the Leiden hiPSC Center (p.7). This center has extensive expertise in hiPSC production and modification. It offers a range of services to support stem cell researchers within Mirai House, across LUMC, and even beyond.

4 Some of the cultivated cells are used in organ-on-chip systems. In specialized labs, researchers create environments that closely mimic conditions in the human body. This allows them to better understand diseases and test potential treatments.

→ *Curious about how a lung-on-chip works? Watch the video here!*



5 To study cells in detail, Mirai House is equipped with state-of-the-art technology. Many advanced instruments are available for shared use among research groups, reducing costs and ensuring access to high-quality tools without the need for each group to purchase their own.

Interested in Mirai House, its research, or facilities? Stop by for a visit – the coffee is ready! ■

A crash-course in regenerative medicine: In Leiden, it's possible!

Regenerative medicine is a societal priority at LUMC, and science communication logically aligns with this. We believe it is important to stimulate curiosity about science, especially among children and young people, so that they are inspired or better understand what science can mean for them. But we also want to reach adults who don't normally come into contact with science. In this way, we aim to increase trust in science and the medical world, and help people form opinions on decisions made by the government, companies, and scientists. In Leiden, there are various opportunities to get to know regenerative medicine.

3 October University

On October 3rd, we celebrate and commemorate the Leiden Remembrance Day, with the entire city participating. Leiden University organizes the Science Market on this day, one of the most enjoyable events of the year. This event connects the city with science and reaches people who otherwise might not be exposed to it. Our researchers enthusiastically share their knowledge of regenerative medicine. They do so using tools such as the Stem Cell Game and an interactive setup with animated videos and physical objects. These were created together with the Dutch Science Agenda. From young to old: everyone learns something new. For example, one visitor understood, thanks to our explanation, why his wife needed a new knee. Critical questions, such as those about the accessibility of expensive treatments, help us better address what people need.

Learn more

Night of Discoveries

During the Night of Discoveries, curiosity and creativity are at the center. This is the perfect place for the reNEW ARTxSCIENCE competition. Within reNEW, researchers from Leiden, Copenhagen, and Melbourne collaborate to conduct stem cell research. They hope to improve the lives of people with chronic diseases. During their work, the researchers, either accidentally or on purpose, create beautiful artworks. The best pieces are submitted by the researchers for the ARTxSCIENCE competition. These artworks are displayed during the Night of Discoveries. Researchers use these pieces to explain stem cells and their research. Visitors discover how stem cells not only help with healing but also can be visually striking.

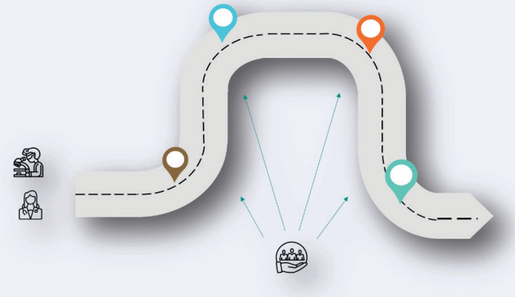
The next edition of the Night of Discoveries will take place on September 20, 2025. ■

Aftermovie Night of Discoveries 2025

Hessel Honkoop, advisor science communication at LUMC: "The research we conduct in regenerative medicine needs to be shared. You have to get people excited. Without public support, scientists won't get far. Fortunately, there are plenty of opportunities to do this in Leiden!"

Lieke van Kempen, Martine de Vries, and Nienke de Graeff – department of Medical Ethics and Health Law

The patient perspective: essential in the development of new therapies!



The development of new therapies and technologies, such as stem cell therapy, gene therapy, organoids, and organ-on-a-chip models, raises ethical questions. It is important to consider these questions early on. As researchers in the Department of Ethics and Law at LUMC, we are actively involved in these developments. In our research, we map out the perspective of patients, an indispensable component. Here, we explain why!

Regenerative medicine

The goal of regenerative medicine is to improve the quality of life for people with diseases or conditions. To achieve this goal, it is important that new therapies align with the needs and wishes of patients. But what are these needs and wishes? To understand this, we must listen carefully to patients. How do they currently experience their disease burden? What are they hoping for in the development of a new therapy? What concerns do they have? And how do they feel about participating in research?

Patient involvement

Involving patients in research on new therapies is not as straightforward as it seems. Often, (lab) researchers and doctors themselves estimate what patients need, based on their own assessments and experiences. The development of new therapies then proceeds in a straight line, without directly asking patients for their thoughts. This can lead to problems, because what if it turns out that patients actually want or need something different? By involving patients early in the research, the "straight line" turns into a route with many more possible detours.

That's why we involve patients early in the research and capture their perspectives through interviews. We interview people with type 1 diabetes and immune disorders, for which stem cell therapies are being developed. We also interview people with hereditary hearing loss, for whom inner ear organoids (sometimes called "mini-organs") are being developed, as well as people with the muscle disease Duchenne, for which gene therapy is being developed.

There are at least four advantages to involving patients in research on new therapies. Patients can tell us (1) which topics and questions they think should be researched, (2) how to measure whether a new therapy is successful, (3) what information they need to decide about participating in research, and (4) whether the therapy would meet their needs and wishes, and what is important in that regard.

The impact of the patient perspective

The results of our research are published in scientific journals and shared with the involved (lab) researchers and doctors. This allows the patient perspective to be immediately used in the development of new therapies at LUMC. Through our research, we hope that regenerative medicine will best meet the needs of the people it is intended for. And we gain new insights for further ethical research. In our view, the patient perspective is indispensable in the development of new therapies and technologies! ■

A day in the life of... *Giorgia Mazzini*

PhD student in the osteoarthritis research group (section Molecular Epidemiology, department Biomedical Data Sciences)

Imagine dealing with pain and stiffness that make everyday activities a challenge – simple movements, once taken for granted, become a daily struggle. This is the reality for millions living with osteoarthritis (OA), one of the most common causes of joint pain and disability. At the Meulenbelt osteoarthritis research group of the LUMC, Giorgia is working on exciting research exploring how stem cells and regenerative medicine could pave the way for desperately needed osteoarthritis treatments. She takes us through a typical day of her life.

07:00 AM Starting the day with focus and care

I start my day at 7:00 AM, usually with a cup of tea and some time with my cat. Taking care of him gives me a moment of calm before the busyness begins. By 8:00 AM, I'm at my desk, planning my day. With experiments to run, meetings to attend, and students to mentor, it's important to stay

09:00 AM Diving into research and mentorship

By 9:00 AM, I'm in the lab, fully immersed in my experiments. I mainly work with induced pluripotent stem cells (hiPSCs), which have the remarkable ability to differentiate into various types of tissue. Our lab has optimized a specialized protocol that directs these cells to mature into cartilage-producing cells. We aim to use these cells to create cartilage implants for transplantation, that can replace lost cartilage in patients with osteoarthritis .

My primary goal, and what keeps me awake at night, is to further optimize the cells to ensure they consistently develop into healthy, cartilage-forming (chondrogenic) cells, starting from hiPSCs and address their scalability. This is particularly important since the cells sometimes lose their cartilage-forming potential over time. My work aims to create a reliable, "off-the-shelf" source of cartilage for transplantation.

The lab work requires great precision and patience. Each step is crucial, and I often find myself in awe of how these microscopic cells hold such potential to revolutionize treatments. In addition to my research, I mentor students, teaching them core techniques and guiding them to feel confident in their lab work. Balancing my own experiments with mentoring can be demanding, but watching students develop their skills is incredibly rewarding.

12:00 PM A break to recharge and connect

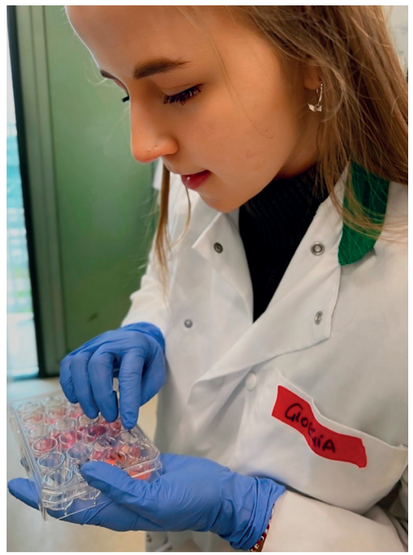
By noon, I'm ready for a break. I head to the canteen for lunch, where I catch up with friends and colleagues from my own and other departments. These casual chats are not only fun – they're often where new ideas are born. Science is so interconnected, and you never know when a conversation might spark an exciting new thought!

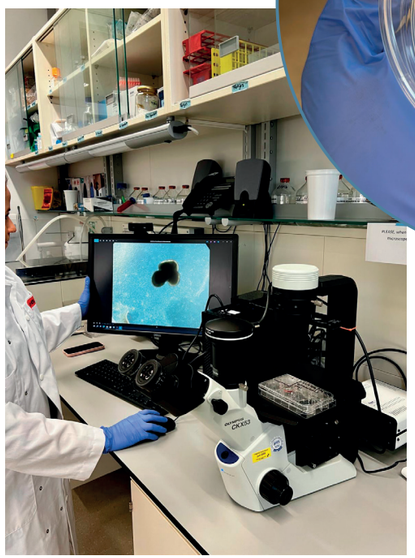
12:30 PM Team meeting

After lunch, it's time for our weekly research group meeting, one of the highlights of my week. We share updates, brainstorm solutions, and set goals for the days ahead. It's incredibly motivating to see how much we contribute to each other's work and inspiring to hear about everyone's progress. While I focus on optimizing cells for cartilage implants, others study the pathways guiding iPSC differentiation into chondrocyte-like cells. Many others have explored mechanical loading and tested human osteochondral explants. Being part of such a passionate and driven group reinforces that, together, we're making real strides toward developing functional iPSC-derived cartilage implants.

1:30 PM Focused research and writing

After the meeting, I focus on desk work. I'm currently optimizing an exciting technique, where we simultaneously look at the accessibility and transcription of the DNA in single cells. This generates a large amount of data that needs to be analyzed through specialized scripts on my computer. With these analyses we seek to unravel molecular insights that explain the difference between good and bad cartilage-producing cells, which is actually a quite tough job.

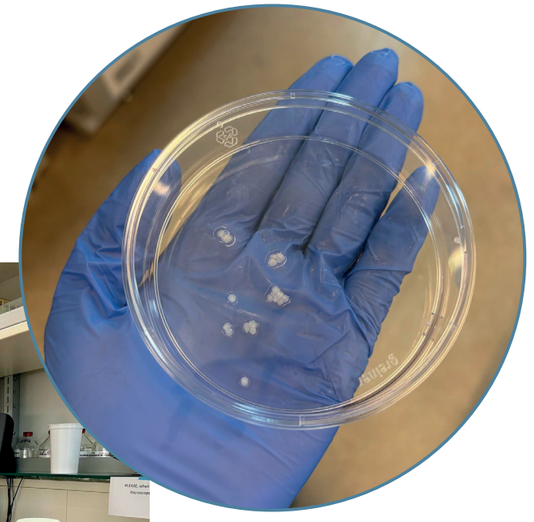




I also write and revise scientific papers, and respond to emails. I carve out time to read the latest articles in regenerative medicine – it's essential to stay updated on what's happening in this dynamic field. Writing is a particularly demanding part of my work, but it's also incredibly fulfilling. Seeing the story take shape and knowing it could contribute to advancing our understanding of osteoarthritis gives me a sense of accomplishment.

6:00 PM Wrapping up and reflecting

By 6:00 PM, I'm ready to wrap up my day and head home. Once there, I lace up my running shoes and head out for a jog. The rhythm of running clears my mind, helping me transition out of "work mode" and recharge. Afterward, I enjoy a quiet dinner while catching up with my family in Italy over a video call – it's always a joy to hear their voices and share a few laughs. Later in the evening, I carve out some time just for myself. I unwind with Netflix, letting myself relax completely and recharge for the challenges ahead. As the day winds down, I reflect on our progress and look forward to what tomorrow brings, knowing that each step takes us closer to impactful discoveries and novel regenerative therapies for OA patients. ■



Setting the bar for micro-physiological systems

Microphysiological systems (MPSs), such as organs-on-a-chip, allow scientists to replicate the structure and physiology of human tissue in the lab. These models can therefore be valuable for studying human disease and testing new drugs. Nevertheless, their similarity with real human organs remains uncertain and large-scale application to drug discovery is limited. Experts from LUMC and other Dutch academic centers affiliated with Netherlands Organ-on-Chip Initiative (NOCI), called for measurable standards that improve MPS reliability in Nature Biomedical Engineering.

"We believe it is time to develop measurable standards that allow us to compare different MPSs directly and assess their relevance to the human body," says professor Christine Mummery. "Only then will MPSs become accepted models for drug testing and disease research."

In their perspective, the researchers propose defining two key aspects of MPS models: *designed* features – such as oxygen levels and fluid flow, which can be precisely controlled – and *emergent* features, like cell behavior, which develop naturally but can be monitored.

By defining standards based on these aspects for various systems like vessel-on-chip, gut-on-chip, brain-on-chip, and heart-on-chip, the researchers provide valuable guidance for scientists working with these models and highlight the importance of standardization. As MPS technology becomes more widely used, this need becomes increasingly urgent.

"With this publication, we emphasize the importance of implementing measurable standards in MPSs. We provide guidance in selecting the right model for each scientific question: specifically, is the model 'fit-for-purpose'? By doing so, we hope to contribute to the implementation of these systems for drug development in the future," concludes Mummery. ■

Read more

Stem cells ready for the clinic

To safely deliver high-quality stem cell therapies to patients, their production must follow strict guidelines known as Good Manufacturing Practice (GMP). In collaboration with researchers from various departments, the LUMC Center for Cell and Gene Therapy (p.7) has now developed a platform that enables the in-house production of human induced pluripotent stem cells (hiPSCs) under these stringent standards. This is a crucial step in making new cell therapies from LUMC available to patients.

GMP production of hiPSCs is complex: it requires a sterile, tightly controlled environment where every step is carefully monitored and documented. Thanks to the new platform, LUMC can now carry out this production within the hospital itself – an achievement that is unique in an academic setting.

"With this platform, we have already produced two batches of hiPSCs, which have been validated and approved for use. We call these batches Master Cell Banks," says Juan Novoa, first author of the study.

These cells can be used to generate various cell types with therapeutic potential, such as pancreatic islets, kidney organoids, heart muscle cells, skin cells, neurons, and inner ear organoids. As such, they play a key role in developing new regenerative treatments at LUMC. ■

Publications

Innovative project to isolate islets of Langerhans for transplantation in patients with type 1 diabetes

Approximately 100,000 people in the Netherlands have been diagnosed with type 1 diabetes. This form of diabetes is an autoimmune disease, meaning that the immune system almost completely destroys the beta cells in the pancreas. As a result, the body produces little to no insulin, causing blood sugar levels to fluctuate significantly. People with this disease must regularly measure their blood sugar and inject insulin to keep it under control.

Beta cell replacement therapy
For some patients, insulin injections are not enough, and their blood sugar levels continue to fluctuate. This can lead to dangerous situations, such as loss of consciousness. These patients often also suffer from other health complications due to type 1 diabetes. For them, a treatment that replaces beta cells could offer a solution. This can be done through a pancreas transplant or by transplanting only the islets of Langerhans, which contain beta cells.

The PancReatic Islet Separation Method (PRISM)
Before transplantation, the islets must be isolated from a donor pancreas. To simplify and optimize this technically complex and time-consuming isolation process, a new technique was developed at LUMC: the PancReatic Islet Separation Method (PRISM) (see box).

LUMC has approved the use of PRISM for clinical applications. Additionally, there is global interest from other hospitals that perform islet transplants. LUMC has partnered with an American company to manufacture PRISM equipment for use in other hospitals. ■

Want to know more about how PRISM was designed? Read about it in *Transplant Talks 2024* (page 6, only in Dutch)

An interview with... Chantal van Litsenburg

From research to therapy: advancing regenerative medicine in an academic hospital

After years in various roles within the pharmaceutical industry, Chantal van Litsenburg decided to take a new direction in 2022, joining LUMC. Here, she is pursuing her dream: contributing to the development of new therapies that are accessible to all patients who need them. "What we aim to do is nearly impossible, but if it can succeed anywhere, it's here."

Her journey began with a conversation with former fellow students Niels Geijsen and Frank Staal – both professors and groupleaders at LUMC. Together, they discussed what is needed to develop medicines effectively within an academic hospital. This conversation planted the seed for establishing a regulatory office at LUMC, dedicated to helping researchers bring new therapies to patients.

Initially, the regulatory office focused on two promising therapies: a new gene therapy for Duchenne Muscular Dystrophy patients in collaboration with prof. Geijsen, and a stem cell gene therapy for young patients with severe congenital immune deficiencies alongside prof. Staal. The latter is a true pioneer in the field, and several patients at LUMC have already received his therapy as part of a clinical study (see also p.13). In the future, the office will support the development of other therapies in a similar way.

A shift in mindset

Developing complex regenerative medicine therapies, such as cell and gene therapies, is a major challenge. It requires extensive expertise and must meet strict regulatory standards. Moreover, academic hospitals are traditionally not set up for medicine development. "Academic hospitals conduct excellent research, but they are not structured for drug development. If we truly want to bring research to patients, we need a different mindset and approach. That's the essence of my role: I'm working to change this mindset."

A unique opportunity

Despite the challenges, Chantal is excited about developments within LUMC. "I strongly believe people eventually make the difference, and here, we have the expertise and experience to make this project a success. People here have a vision and are willing to break through walls to achieve it. That's incredible."

She adds that working in an academic hospital offers unique opportunities compared to the pharmaceutical industry. "The great thing about this environment is that we can develop therapies that aren't immediately commercially attractive. The diseases we focus on are often rare or at least technologically complex. We have more time to solve the puzzle – but we must use that time wisely."

Building bridges

Chantal and the regulatory office play a crucial role in ensuring this efficiency. "Together with researchers, we build a bridge while walking across it. We continuously refine our vision of the other side – identifying requirements and essential building blocks along the way."

By carefully planning crucial steps, the team prevents late-stage obstacles that could force researchers to restart or even halt development. This ensures therapies reach patients as quickly as possible. "In practice, I seek advice from the regulatory agencies that will eventually approve new medicines. I also ensure our therapies receive 'orphan drug' designation, which provides financial and regulatory benefits for medicines targeting rare diseases."

> *"What I enjoy most is involving people from research projects directly in our work. These are the key players who will make the projects succeed. In the future, I hope it will become standard practice that every new therapy developed at LUMC has someone bridging research and the regulatory office."*

Teamwork is key

Chantal is not working alone. At LUMC, experts from various fields – researchers, clinicians, pharmacologists, and ethicists – collaborate closely. For example, she works with the LUMC Center for Cell and Gene Therapy (p.7), where Pauline Meij and her team already produce regenerative therapies at small-scale while ensuring they meet all necessary standards.

Together with her colleague Yuxi Zhao, Chantal is also working to engage more researchers in the regulatory office's efforts. "What I enjoy most is involving people from research projects directly in our work. These are the key players who will make the projects succeed. In the future, I hope it will become standard practice that every new therapy developed at LUMC has someone bridging research and the regulatory office."

The end goal

"We want to advance some of our therapies beyond clinical trials – into treatments that reach all patients in need. To achieve this, we must build strong regulatory dossiers and follow a structured development process." These therapies can serve as blueprints for future medicine development at LUMC. "If researchers in the future automatically turn to the regulatory office for expert advice and support, my mission will be accomplished. That's my goal: to establish this as a lasting framework." ■

Stem cell islets: a future for patients with Type 1 Diabetes?

Scientists may be one step closer to a functional cure for type 1 diabetes (T1D). Recently, Chinese researchers demonstrated for the first time that insulin-producing cells, generated from a patient's own stem cells, can be successfully transplanted and functionally cure a patient. This breakthrough could eliminate the need for lifelong insulin injections.

T1D is an autoimmune disease that destroys insulin-producing cells in the pancreas and affects millions of people worldwide. Currently, the only curative treatment is a donor pancreas or, less invasive, islet transplantation. The LUMC is the only university hospital in the Netherlands performing islet transplantations, but it still relies on scarce donor organs. To overcome this limitation, scientists are exploring how to create insulin-producing islets from stem cells.

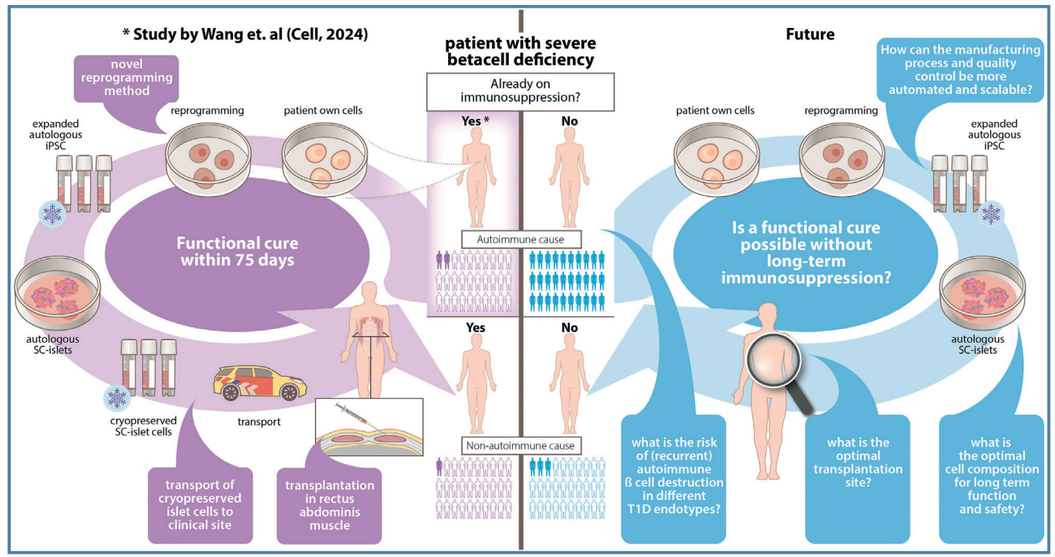
Professor Eelco de Koning and associate professor Françoise Carlotti from LUMC discuss the future of stem cell islets in a commentary published in Cell Stem Cell. They analyze the Chinese study and the two main research directions: off-the-shelf stem cell islets, which can be mass-produced, and personalized "self" islets derived from a patient's own stem cells. The first option is scalable and economically promising but requires immunosuppressive medication. The Chinese study indicates that "self" islets can be used, but questions remain.

"The patient in this study was already on immunosuppressive medication due to a previous transplant," De Koning explains. "We need to investigate whether transplants with these 'self' islets can succeed without such medication."

Future research, including that of De Koning and Carlotti at LUMC, will determine if and how stem cell islets can offer a future without insulin injections for T1D patients worldwide. ■

Read more here

Want to know more about De Koning's research?



Human kidney organoids integrate into mouse kidney using a novel transplant model. Photo: Rianne van Nieuwland and dr. Cathelijne van den Berg

LUMC RegMed

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REGENERATIVE MEDICINE AT LUMC