Transforming lives with stem cell medicine
Life in the making: decoding infertility with blastoids
Roughly one in six people globally are affected by infertility, with most unsuccessful pregnancies failing within the first week after conception. Our goal is to model the initial stages of human development using stem cells to uncover what can go wrong during this critical phase and to better understand the underlying causes of early pregnancy loss.

Photo: Antar Drews, PhD fellow, Jan Żylicz’s lab, reNEW Copenhagen, winner of the ARTxSCIENCE competition.
Message from the CEO

Reaching flight altitude

I am pleased to be able to present our second Annual Report summarizing our progress within the Novo Nordisk Foundation Center for Stem Cell Medicine in 2023. In the pages that follow, you will be able to read about last year’s achievements and celebrate the wonderful research outcomes our teams have driven.

After an incredible launch in 2022, we are reaching flight altitude, and 2023 was another great year of stem cell science and translation. reNEW supports excellent stem cell researchers to develop products. It is with considerable excitement that we have seen Associate Professor Agnete Kirkeby and her Lund team reach phase 1/2a clinical trial for the treatment of Parkinson’s disease via the injection of human embryonic stem cell-derived dopaminergic neurons. While representing the culmination of 13 years in development, Agnete’s team is continuing to progress other neural advanced therapy medicinal products (ATMPs) for a variety of chronic neurological diseases.

With the RAG-1 SCID trial commencing in Leiden in 2021, Professor Frank Staal is continuing to work on RAG-1 SCID with the support of reNEW. reNEW has also supported the establishment of a clinical trial site in Melbourne to enable clinical delivery at that node. Our major disease teams, including heart, kidney, pancreas, and muscle, are all progressing well. We have also established our first adult stem cell disease team focused on delivering patient intestinal stem cells for the treatment of ulcerative colitis. Our EXPLORE research is also generating intellectual property upon which the next translational opportunities can be developed.

Sadly, we have also lost one of our own. On December 15, Professor Palle Serup passed away after a long battle with cancer. We thank Palle for his long contribution to our understanding of pancreas development and the subsequent optimization of pluripotent stem cell differentiation to beta islet cells. Our work on diabetes continues across all three reNEW nodes.

Nineteen researchers and administrative staff joined reNEW in 2023, supported by an increased deployment of underpinning and targeted research funding to all groups. As a result, a large focus for 2023 has been on internal collaboration, ensuring that the researchers on the ground at all sites align with our Vision. A part of that is enabling them to communicate and collaborate with each other, irrespective of location. Importantly, this supports our objectives around training and capacity building, as well creating an international critical mass in stem cells.

To enable this, we launched reNEWConnect as an internal portal of information on research, training, and engagement opportunities in June 2023. This online portal complements reNEWS, our internal communication newsletter launched in 2022. We are now at issue 16 of reNEWS, which since last year also is delivered to our external network. The visibility of reNEW has continued to grow, particularly supported by a very busy social media network. Alongside the external facing website, reNEWS and reNEWConnect provide many avenues for communication. Globally, we have supported the creation of an international Early Career Researcher committee with membership drawn from all sites. This group has developed its own set of communication and outreach opportunities to bring researchers together.

I would thank every person who has contributed to reNEW in 2023, I would also acknowledge the incredible support of the partners in the venture – the University of Copenhagen, the Leiden University Medical Center and the Murdoch Children’s Research Institute – and thank them for hosting reNEW. I would also thank the Novo Nordisk Foundation for their faith in our Vision and in myself, but also for their unwavering support and advocacy on our behalf.

reNEW will continue to support the best stem cell research and stem cell researchers at each site, incentivize those researchers to consider what their research might be able to do to help people, and remove the barriers to taking good science to targeted outcomes.

“After an incredible launch in 2022, we are reaching flight altitude, and 2023 was another great year of stem cell science and translation.”

CEO of reNEW
Professor Melissa H. Little
Message from the reNEw Governance Committee

Building from each other to future therapies

Our second year of partnership across the reNEw consortium has seen amazing growth, collaboration, and leverage. In a short period of time, our researchers at all nodes have initiated genuine research partnerships that bring together complementary expertise to address critical health challenges. The visibility of reNEw globally has significantly grown and, as a result, the reputation of our institutions in the stem cell field along with it. Early clinical outcomes are particularly exciting, as is the protection of novel intellectual property in the stem cell space from our researchers. We are also very pleased to see a unity of purpose that draws in everyone from the students to the most senior scientists, as well as the administration, operations, and facility staff.

In 2023, we as representatives of the partners have had opportunities to visit each other and hear about the science of researchers at nodes other than our own. We applaud the strong alignment of our researchers with the strategy and have universally seen additional opportunities in the relationships between our organizations. As such we look forward to strengthening these links over the coming years.

The oversight of reNEw involves the contribution of many, with a variety of governance bodies providing valuable input. We thank the members of the Scientific Advisory Committee, all of whom are stellar researchers across the fields of basic and applied stem cell research. We are grateful for the support of the Development Advisory Committee, drawn from our own organizations, which provides input on intellectual property management and business development. We also thank the Novo Nordisk Foundation, which has generously contributed not only to the funding, but also to the advocacy of reNEw since its inception. The ongoing investment of the Novo Nordisk Foundation in the stem cell field, notably with the announcement of the NNF Cellerator to be constructed in Copenhagen by 2027, has also provided an additional opportunity for reNEw to translate its concepts into outcomes.

As the members of the Governance Committee of reNEw, we remain excited by and committed to the Vision and look forward to the years to come.
Working across the globe to deliver across the disease

Within reNEW, we believe that stem cell medicine represents a huge opportunity for the development of new treatments for currently untreated conditions. This can include improved drug development, cells, and tissues into patients and stem cell gene modification to address underlying disease causes.

reNEW is a global consortium focusing on stem cell research involving three leading research institutions: the University of Copenhagen in Denmark, the Leiden University Medical Center in the Netherlands, and the Murdoch Children’s Research Institute in Australia. Our researchers work across many tissues of the body to reach our Vision and Mission.

Learn more about the diseases we work on and the organ systems affected at www.renew.science.

**OUR VISION:** to create a new generation of effective, safe, and socially sustainable stem cell-based therapies built on an international collaborative network of excellence in targeted biomedical research.

**OUR MISSION:** to develop an international targeted research center delivering innovative stem cell-driven therapies to transform the lives of people suffering from incurable disease.
Strategy
Ensuring impact

Achieving the Vision and Mission of reNEW will require delivery against six key strategic objectives. This Annual Report presents our activities and successes in 2023 against these strategic objectives.

1. Create a unique and world-leading international research center that provides new or enhanced opportunities for achieving synergies that will foster research excellence and advance stem cell medicine
   
   SEE PAGE 15

2. Mitigate barriers and nourish an academic culture where excellent stem cell researchers are motivated to pivot to translation and innovation
   
   SEE PAGE 26

3. Deliver the next generation of talented young researchers who are educated, trained, and mentored in basic research, clinical translation, and commercial development of stem cell medicine
   
   SEE PAGE 44

4. Grow the next generation of stem cell medicine products in a vibrant international collaboration spanning disease, technology, and product type
   
   SEE PAGE 50

5. Build bridges between the research, clinical, regulatory, and commercial sector, and the community to prepare society for stem cell medicine therapies and deliver translational outcomes
   
   SEE PAGE 56

6. Grow jobs and create businesses in stem cell medicine at all three nodes to deliver novel treatments for disease using stem cells
   
   SEE PAGE 64
A global partnership built on excellence

The Novo Nordisk Foundation Center for Stem Cell Medicine, reNEW, represents a huge opportunity to address chronic disease, as well as untreatable inherited disease. This spans the delivery of stem cell-derived cells for tissue regeneration to the modeling of human tissues for drug development. Our unique global collaboration, involving the partnership between the University of Copenhagen in Denmark, the Leiden University Medical Center in the Netherlands, and the Murdoch Children’s Research Institute in Australia, is anchored on research excellence in stem cell biology. This excellence includes the cutting-edge facilities present at each site.

reNEW Copenhagen has demonstrated a depth and breadth of research excellence in 2023 that we can be very proud of. Located within the Faculty of Health and Medical Sciences at the University of Copenhagen, our principal investigators were awarded four European Research Council (ERC) awards, including a starting, a consolidator, and two advanced grants. (See p. 25).

“As we enter our third year in operation in Copenhagen, it is fabulous to see such a high-quality research unit strongly aligned with the Vision of reNEW,” commented Professor Melissa H. Little in her role as node director in Copenhagen.

This quality is evident from the high-impact publications published last year, including seminal contributions to the understanding of colonic progenitor expansion, mechanobiology within respiratory epithelium, and transcriptional changes during early patterning. Our EXPLORE research has generated intellectual property around media and differentiation protocols of relevance to adult stem cell expansion, maintenance of pluripotency, and metabolic regulation of trophoblast identity. Our targeted research portfolio has also begun to mature with the first transition from a proof of concept to a disease team to deliver autologous colonic stem cells for the treatment of ulcerative colitis. The immense contribution of Associate Professor Agnete Kirkeby to cell therapies for Parkinson’s disease culminated in the treatment of the first patients in Sweden. Within reNEW, her team is developing additional cell types for the treatment of dementia. In collaboration with the Novo Nordisk Foundation Cellerator, our teams are now working toward cell manufacturing for several cell therapy projects.

“The incredible global visibility that reNEW has brought to the University of Copenhagen, and to our researchers at all stages of their careers, has really reinforced Denmark as the place to do stem cell science,” Little said.

The heart of the Copenhagen node is our people. With support from reNEW, we have been able to support international exchanges, conference attendance, and translation training for many of our staff and students. The vibrant engagement opportunities closer to home, including the Copenhagen Culture Night and the ARTxSCIENCE competition, have enabled us to reach the community around our research.

“Last year also brought sadness with the passing of Palle Serup. A gentle giant in the field of pancreas biology, Palle worked until the end to enable his team. His contribution to science, both during his time with the Hagedorn Institute and Danstem prior to reNEW, represents a legacy that will endure into the future,” Little said.

The University of Copenhagen also hosts the reNEW Hub. While a major role for the Hub is the central oversight of financial and research reporting, our hub staff also coordinate the global activities of reNEW, including all reNEW governance, annual scientific meetings, collaborative, and targeted funding opportunities, coordination of global communication and engagement, coordination of all research management and reporting, and the management of funding for theme activities, conference attendance, outreach, and exchange. With the expansion of the node, the reNEW Hub has relocated to separate offices on campus. Our staffing expanded at the end of 2023 and will expand further in 2024 to support the internal financial oversight of the hub and the node.
Research update from reNEW Leiden

reNEW Leiden is located within the Leiden University Medical Center (LUMC) in the Netherlands. Regenerative medicine has a prominent position within the organization, which is reflected by the fact that it is one of its three societal outreach areas. LUMC's work is strongly connected to the vibrant life science ecosystem at the Leiden Bio Science Park that focuses on regenerative medicine and has long-standing collaborations with nearby industry to bring innovative stem cell-based therapies to the clinic.

"Over the last year, reNEW has been a real boost not only to the research in our node, but to the entire regenerative medicine ecosystem in Leiden. Our events, such as TechTalks, workshops, UniStem Day, and Stem Cell Awareness Day, have stimulated existing and new collaborations and enforced our position in the field of stem cell-based medicine," said Professor Ton Rabelink, reNEW Leiden's node director.

The targeted proof of concepts and disease teams running at the Leiden node took off in 2023 and researchers from reNEW Leiden visited their colleagues in Melbourne and Copenhagen. In addition, research within reNEW's EXPLORE theme has resulted in high-impact publications.

"The international nature of reNEW has taken the projects at our Leiden node to a higher level. Our collaborators at the Murdoch Children's Research Institute and University of Copenhagen have provided valuable knowledge and expertise needed to bring our research closer to the clinic and impact the lives of patients in the future," said Rabelink.

"A great example of this is the extension of the RAG-1 SCID clinical trial from Leiden to Melbourne, made possible through collaborative funding of DKK 6.2 million (EUR 800,000) from reNEW. Children with RAG-1 SCID are born without infection-fighting immune cells; without treatment, most children die from infection during their first or second year. The Australian arm of this trial will be led by reNEW Melbourne's Associate Investigator, Associate Professor Rachel Conyers. The trial will provide eligible RAG-1 SCID children with a working copy of the RAG-1 gene, meaning they will likely be able to build a healthy immune system and live a normal life.

Across the year, reNEW Melbourne has worked to build connections with the broader community, from our involvement in UniStem Day with high school students, to participating in Australasian Society for Stem Cell Research public forum. Our contributions to the reNEW ARTxSCIENCE competition showcased the beauty of our science and the impact we hope to have on research and its translation into the clinic.

Looking ahead to 2024, reNEW Melbourne remains dedicated to not only advancing stem cell medicine but also ensuring that our research is accessible to the public. We look forward to continuing to advance our stem cell science and translation through international collaboration, enabled by reNEW.
Driving outcomes supported by state-of-the-art facilities

To reinforce the global capacity of our collaboration, reNEW supports distinct technology platforms at each node. By enabling access to and training on these technologies across all sites, we mutually enhance the quality of all our research.

reNEW Copenhagen

Genomics platform

The genomics platform offers next-generation sequencing (NGS) support and service-based Illumina and Oxford Nanopore technologies. It provides a high-throughput, tailored sequencing service and operates as a train-to-sequence and ready-to-sequence service. Users are trained to prepare their sequencing libraries with the help of the expert staff present on the platform. They also provide training in bioinformatics techniques and run peer-learning activities across sites and within the host organization. Besides access to classical sequencing methods, the platform hosts a spatial transcriptomics setup from Resolve Biosciences.

Imaging platform

The imaging platform provides state-of-the-art light microscopy equipment, project consulting, assay design, image analysis, training, and assistance as required by researchers to visualize and measure fluorescently labeled structures in cells and tissues. Support in a wide range of light microscopy applications, such as widefield and confocal microscopy and quantitative image and data analysis, is an integral part of the platform’s offering. Within this reporting period, the platform introduced enhanced high-throughput microscopy and screening capabilities within a local IFD-funded stem cell consortium.

Flow cytometry platform

The flow cytometry platform is a shared resource laboratory operated by reNEW and the NNF Center for Protein Research (CPR). The facility has state-of-the-art equipment and software for cell sorting and analysis, including the recent advance in image-enabled cell sorting technology. Besides supporting sorting and analysis campaigns, the platform provides training and support in experiment design to researchers, especially maximizing the novel image sorting capabilities for screening campaigns.
hiPSC hotel

Research groups can bring their tissue to this human induced pluripotent stem cells (hiPSC) hotel, where the team can isolate the somatic cells from different tissues, perform reprogramming with state-of-the-art vectors, and do basic characterization of pluripotency. They also generate isogenic control hiPSCs using CRISPR/Cas9 technology. The hotel also provides validated differentiation protocols and extensively characterized control hiPSCs.

Center for Cell and Gene therapy

The Center for Cell and Gene therapy (CCG) facilitates the development and production of advanced therapy medicinal products (ATMPs) and challenge agents. The center also offers expertise in translational drug development, notably the regulations of ATMPs, challenge agents, and other innovative products for clinical use. In addition, the CCG provides manufacturing and release services for investigational medical products under good manufacturing practices (GMP).

Organ-on-chip center

The Organ-on-Chip (OoC) center has a wide range of commercial OoC systems available to researchers wishing to examine the value of these systems prior to possible purchase from vendors or to carry out a defined set of experiments in the facility. HPSC derivatives and bespoke OoC models can also be beta-tested here. Finally, there are training opportunities for academics and company R&D personnel in individual hands-on settings/multiparticipant courses.
The Stafford Fox Drug Discovery Facility (SF-DDF) offers a platform for high-throughput and high-content phenotypic drug screening using iPSC-derived tissue-specific cells and organoids. Its objective is to enable automation of complex human models of disease to accelerate the identification of new drug-like compounds for the treatment of inherited genetic diseases.

The Bioinformatics Hub offers end-to-end bioinformatics support to all reNEW labs. Its vision is to work with researchers from design to publication. Through co-design and collaboration, the Bioinformatics Hub can provide bespoke analysis of their bulk, single-cell, and spatial transcriptomics datasets. The group has extensive experience in analyses and integration of multi-omics data (epigenomics, transcriptomics, proteomics, DNA methylation). It also supports data analytics and visualization through dedicated internal web servers (Galaxy, Degust, Virtual Reality Exploratory, and Analytical Tools).

The iPSC derivation and gene editing facility provides stem cell derivation and gene-editing services to researchers worldwide. Its staff generates standard and gene-edited iPSC lines in feeder-free and chemically-defined medium in a fast and cost-effective manner. The facility can also perform gene editing in already existing iPSC lines, as well as the generation of lineage-specific reporter lines.

The small molecule compound library for drug discovery empowers researchers with the tools to drive drug discovery initiatives. It centers on the acquisition and management of a custom designed compound library, crafted to cater to the specific needs of reNEW’s researchers. It currently stores a bespoke library of 30,000 small molecules with drug-like properties. (See p. 50)
High-quality publications

The hard work carried out by the researchers at reNEW’s three nodes resulted in 76 published articles during 2023. A selection is listed below:

**UCPH**


**LUMC**


**MCRI**


- Associate Professor Silvia Velasco and her team from reNEW Melbourne were awarded a 2.8 million Australian dollar five-year NHMRC investigator grant by the Australian National Health and Medical Research Council (NHMRC) to investigate the biological causes of autism spectrum disorder using brain organoids, which model early human brain development.

- Professor Christine Mummery from reNEW Leiden was awarded the 2023 ISSCR Public Service Award by the International Society for Stem Cell Research (ISSCR) for her dedication, leadership, and advocacy in stem cell research, as well as her tireless support of female scientists.

- Professor Joshua Brickman and his team from reNEW Copenhagen were awarded a 2.5 million euro five-year advanced grant by the ERC for their work on unraveling the specificity of epi-metabolic regulation in development.

- Professor Klaus Hoeyer and his team from reNEW Copenhagen were awarded a 2.5 million euro five-year advanced grant by the ERC for their focus on the implications of sharing sensitive health data across borders, and how individuals and health professionals view and experience this potentially privacy-infringing development.

- Associate Professor Jakub Sedzinski and his team from reNEW Copenhagen were awarded a 2 million euro five-year ERC consolidator grant for their work on understanding how mechanical forces regulate embryo development. They will analyze how cells perceive mechanical cues from their tissue environment.

- reNEW’s CEO, Professor Melissa H. Little was appointed Companion of the Order of Australia for her significant contribution to Australia’s health and medical research landscape.

The hard work carried out by the researchers at reNEW’s three nodes resulted in 76 published articles during 2023. A selection is listed below:

**UCPH**


**LUMC**


**MCRI**


Embryonic frog skin model provides new clues to asthma treatments

The development of our airways has puzzled scientists for years. Researchers at the reNEW Copenhagen node have now provided a comprehensive model explaining how respiratory tissues are formed by analyzing how stem cells develop in frog embryos. These results could help find treatments for respiratory diseases.

The research is based on the development of frogs’ embryonic skin, which shares many similarities with the respiratory tissues of mammals, including those of humans. Contrary to previous studies of respiratory tissues that primarily focused on the regeneration and repair of cells, reNEW’s Associate Professor Jakub Sedzinski, in collaboration with Associate Professor Kedar Natarajan from the Technical University of Denmark, analyzed the developmental process of the respiratory tissue.

“By dissecting the complex interactions between the mucus, cilia, and other epithelial cells in the airways, we gained insights into how the airways and respiratory diseases develop,” Sedzinski said.

The researchers were able to track the development of the different cell types found in the respiratory tissues and see how they matured over time, using bioinformatics analysis and imaging techniques. Their results can now be used to study the effects of both genetic and environmental factors on cellular dynamics during the development of airways.

“With this knowledge, we can work toward the development of regenerative stem cell therapies aimed at restoring the function of damaged airways, which is important for treating respiratory diseases, such as asthma and chronic obstructive pulmonary disease COPD,” Sedzinski added.

Their work greatly matters as more than 500 million people worldwide suffer from chronic respiratory illness. And this number is likely to rise over the coming years due to the environmental pollution surrounding us.

The next step in the research of the Sedzinski lab is to understand how to manipulate the described developmental program to drive the formation of specific cell types and regulate their maturation.

“We aim to understand the spatial distribution of the identified genes so that we can determine when and where they are active during specific cell type development. This will provide us with important insights into the signaling pathways and molecular mechanisms that drive cellular differentiation and tissue patterning,” Sedzinski said.

Our basic research portfolio, EXPLORE, continues to drive the ideas that can be further developed within our targeted portfolio, while reBUILD, reSOLVE, and reWRITE deliver new treatments. Our social research team, PREPARE works alongside these teams to address barriers to acceptance and balance expectations in the community.
Monkeypox infections & treatments modeled in skin organoids

The recent global outbreak of monkeypox has put this unpleasant viral disease in the spotlight. Researchers at the reNEW Leiden node have since successfully modeled monkeypox infections in skin organoids derived from human stem cells. These organoids are now being used to test potential new treatments.

The skin is the largest organ of the human body. When healthy and functioning properly, the skin creates an efficient barrier. It not only provides us with protection from external factors such as UV radiation or air pollution, but also from pathogens, such as bacteria and viruses.

A virus that causes skin problems in the form of lesions is the Mpox virus, formerly known as monkeypox. In 2022, a global outbreak caused a worldwide stir as patients exhibited more severe symptoms than those usually reported in Central and West Africa, where the disease is endemic.

Research on the Mpox virus has traditionally used cultured human cell lines or animal models. reNEW Leiden’s Dr. Karine Raymond, Dr. Spiros Pachis, postdoc in her group, and collaborators from Dr. Qiuwei Pan’s lab at the Erasmus Medical Center in Rotterdam instead generated 3D human skin organoid tissues to study viral infection. Their model can replicate the key structural and functional features of human skin, facilitating the study of viral infections. “This opens up exciting potential research avenues aiming at uncovering more insights on what actually happens when the Mpox virus or any other pathogen that affects the skin infects patients,” Raymond said.

The researchers managed to capture and visualize all stages of the life cycle of the Mpox virus by using a technique called transmission electron microscopy. When examining the infection’s effects on the expression of genes in the skin organoid cells, they observed extensive alterations compared to the uninfected control cells. These included both changes in genes that encode for proteins with a structural or barrier function role in the skin, as well as in molecules normally produced by skin cells when exposed to some form of stress.

The generated skin organoids have also been used to test potential new treatments. The effectiveness of a promising antiviral drug candidate against the Mpox virus was confirmed by Raymond and her team. “We found that administering it at different timepoints during the infection process significantly inhibited the production of new viruses and prevented the gene expression alterations from taking place,” she said.

Brain organoid models used to understand abnormalities that lead to autism, ADHD

The development of the human brain, and specifically the cerebral cortex, is one of the most remarkable evolutionary processes. Its complexity underpins advanced cognitive and motor tasks distinct to humans.

Human brain development largely occurs in utero and is therefore inaccessible for investigation. Most of what we know about this process comes from studies in animals. However, many aspects of human brain development are not shared with other animals and therefore, we cannot entirely understand human brain development using animal models.

To overcome this, Associate Professor Silvia Velasco from reNEW Melbourne has used pluripotent stem cells to create brain organoid models that closely mimic the cellular complexity, anatomy, and function of the developing human cerebral cortex and other brain regions important for cognitive functions.

Using these models, the Velasco lab, based at the Murdoch Children’s Research Institute, aims to understand more about the cellular and molecular basis of human brain development and childhood brain diseases.

The team is exploring how abnormalities during brain development lead to neurodevelopmental disorders, a large group of neurological conditions, which include autism spectrum disorders, intellectual disabilities, attention deficit hyperactivity disorders, and infantile epilepsies.

Current treatments for these conditions are inadequate and designed to manage lifelong symptoms. The team aims to identify cell types affected, molecular targets, and specific functional abnormalities that will give insights into the disease mechanisms of these neurological disorders. This will be instrumental to contribute to the development of new therapeutic strategies for these conditions, for which no effective treatment is currently available.
Targeted research across the globe

The reNEW targeted research portfolio has continued to expand with new proof of concept (POC) and disease teams (DT) in Copenhagen and Melbourne.

31 grants initiated within our targeted portfolio
24 two-year proof of concept projects
7 five-year disease team grants
Congenital heart disease (CHD) is a group of birth defects that cause structural malformations of the heart, heart valves, or major blood vessels. Babies born with CHD face significant health challenges, including increased risk of heart failure. Sadly, CHD is one of the leading causes of infant mortality.

Surgical advances have dramatically increased survival rates over the past 40 years, with more than 85 percent of children with CHD now living into adulthood. However, there has recently been a sharp rise in the number of individuals with underlying CHD hospitalized due to heart failure. Traditional heart failure therapies may not offer the same benefit in people with underlying CHD, and they are often poor candidates for heart transplantation. Even for those who receive a heart transplant, half do not survive 10 years post-transplantation.

Professor Enzo Porrello, the node director at reNEW Melbourne, leads an interdisciplinary disease team developing bioengineered human heart tissue from pluripotent stem cells. This team consists of reNEW researchers Associate Professor David Elliott, Professor Megan Munsie, and Dr. Wilbert B. van den Hout, scientists from other medical research institutions including key collaborator Professor James Hudson from QIMR Berghofer, as well as clinicians from the Royal Children's Hospital in Melbourne.

Bioengineered human heart tissue has the potential to delay or prevent the need for heart transplantation in people with heart failure, including those with CHD. “What we are working on could be transformative,” Porrello said. “Currently, the only option for children or adults who develop heart failure and who are not responding to standard drug therapies is to place them on a heart transplant waiting list with mechanical support provided as a bridge to heart transplantation.”

reNEW funding has brought together this disease team with complementary skill sets and technologies to drive this work from discovery research toward clinical translation. The team is refining their bioengineered human heart tissue to determine its potential as a new therapy, including currently testing it in a clinically relevant large animal heart failure model.

The team also maps regulatory pathways, undertakes health economic evaluations, and scopes ethical issues relevant to the commercialization and clinical translation of this technology. These studies will pave the way for clinical trials in humans. “Our hope is that bioengineered heart tissues will one day provide an alternative to heart transplantation in heart failure patients with underlying CHD,” said Porrello.
Stem cell research pivoting to outcome

Can suffer symptoms along the entire digestive tract disease, the other major variant of inflammatory bowel disease, and inflammation confined to the colon. Patients with Crohn’s disease (IBD), affects around 0.6 percent of the population in Denmark. Patients with ulcerative colitis are affected by ulceration and inflammation confined to the colon. Patients with Crohn’s disease, the other major variant of inflammatory bowel disease, can suffer symptoms along the entire digestive tract.

Typically diagnosed between 15 and 30 years old, patients with ulcerative colitis at present face a lifetime on anti-inflammatory medications, as there are no curative options. Roughly half of patients receive first-line treatment options, but increasing numbers are being transferred onto expensive, second-line biologic, and new small molecule alternatives. A large fraction of the patients on second-line options either do not respond or become insensitive to these treatments. There is consequently a large patient group in need of an alternative.

Professor Kim Bak Jensen from the reNEW Copenhagen node is one of the patients on second-line options who is in need of an alternative. “We are working to not only eliminate the inflammation, but also heal by itself” said Jensen. “We are working to not only eliminate the inflammation, but also heal by itself.”

Images from colonoscopy examinations of patients with ulcerative colitis show that large areas of the mucosa, the soft tissue that lines the bowel, have been lost. Without this lining, made up primarily of epithelium, the body is exposed to the trillions of bacteria residing in the lumen of the colon, leading to sustained inflammation. The current symptomatic treatments available suppress the inflammation, leaving the epithelium to heal by itself.

“We are working to not only eliminate the inflammation, but also help the mucosal lining reform efficiently. From small biopsies, we can isolate single epithelial cells, which we can grow into organoids consisting of thousands of cells. The idea is that organoids infused into the colon will form a living bandage that will contribute to tissue regeneration and rapidly form a mucosal layer, thereby eliminating the constant exposure to luminal antigen and bacteria and reducing inflammation. We believe that our optimized methodology will allow us to grow enough organoids to generate this bandage within two to three weeks,” said Jensen.

Currently, the disease team is moving from growing organoids in the lab in semi-rigid conditions, to developing standard operating procedures for the cellular therapy. To reach clinical trial, every component and procedure within the protocol must be carefully scrutinized to ensure the safety of the product.

Although expensive, cellular therapy can be curative, and I hope that with the development of this therapy we’ll be able to help relieve some patients of their debilitating symptoms. That’s my dream,” said Jensen.

Diabetes mellitus affects 450 million people worldwide. Ten percent of patients have type 1 diabetes. In these patients, insulin-producing beta cells that normally reside in cellular structures of the pancreas, called islets of Langerhans, are destroyed by the immune system. To survive, this group must regularly inject themselves with insulin to normalize glucose levels in the blood.

Type 1 diabetes usually occurs during childhood or young adulthood, has a significant impact on the daily lives of patients, and is responsible for considerably more than 10 percent of all direct and indirect diabetes-related costs to society, presenting a huge unmet clinical and societal need for new therapies.

Beta cell replacement therapy is the only therapy that normalizes glycemia without a risk of hypoglycemia - when glucose levels in the blood drop too low. However, resulting from a shortage of donors, access to this current therapy will always remain limited. Due to the progressive loss of beta cells, it has also been found that the majority of patients lose insulin independence within five years of the transplant, even if they achieved this after the islet transplantation.

Following 15 years of clinical islet transplantation and research into human islet biology, Professor Eelco de Koning from the reNEW Leiden node has been awarded a targeted disease team project grant. De Koning and his team will use this grant over the next five years to pave the way for the next generation of beta cell replacement therapies by using human pluripotent stem cells to generate insulin-producing cells.

“With stem cells we can potentially generate billions of insulin-producing cells for thousands of patients rather than being dependent on a couple of hundred donors,” said de Koning.

The disease team will generate stem cell derived islets that can be used for clinical transplantation in patients with diabetes. This will be performed in a Good Manufacturing Practices (GMP) environment, which is a specialized laboratory in which cell products for patients can be made. By identifying biomarkers, the disease team is currently assessing the risks associated with this therapy, such as suboptimal function and malignant transformation of the cells.

“Of course, the cells need to be safe, and they need to function well, and that is being tested now. Within this program, we will manufacture a clinical-grade islet cell product that is ready for a first-in-man trial at the Leiden University Medical Center. What is exciting is that we are really at the doorstep of these novel stem cell therapies,” said de Koning.
Using human stem cell-derived models of diseased tissues, reSOLVE’s targeted projects are improving the development of drugs for a wide variety of inherited and chronic diseases. Many of these proof of concept projects are reaching compound screening.

Identifying new treatments for Facioscapulohumeral muscular dystrophy

Associate Professor Richard Mills at reNEW Melbourne is an expert at growing models of skeletal muscle from stem cells in a dish. These bioengineered skeletal muscles can act and function like the muscles in our bodies. These models give us the unique ability to elucidate important properties like muscle strength and endurance.

Mills and his collaborators across Australia have used these lab-grown skeletal muscles to model a genetic muscle disorder called Facioscapulohumeral muscular dystrophy (FSHD). The disease is characterized by a progressive degeneration and weakness of skeletal muscles in the neck, head, and shoulders. It is estimated to affect up to 1 in 8,000 individuals globally.

Whilst the life expectancy of people living with FSHD is normal, the deterioration of muscle mass and function limits their ability to move independently and reduces their quality of life. There are currently no treatments for FSHD at hand.

The muscle models of FSHD grown by Mills show the same muscle degeneration seen in the muscles of people living with FSHD. This, paired with other analyses, has demonstrated that their model in a dish represents key features of the disease.

Through a pilot project funded by reNEW, Mills and his team will work with the reNEW Drug Discovery Facility based at the Murdoch Children’s Research Institute in Melbourne. They will screen 30,000 drug compounds against their FSHD models with the aim of identifying drugs that prevent, or at least reduce, the decline of muscle strength and function in FSHD.

Access to this compound library was made possible through the global research partnership with Compounds Australia, a facility that stores small molecules. reNEW has a curated list of 30,000 small molecules that are available to all reNEW researchers. (See p. 50)
Stem cell research pivoting to outcome

A vascularized heart-on-chip model made from human induced pluripotent stem cells (hiPSCs) has been developed by the reNEW Leiden node. The model showed that continuous flow of fluid through laminarized tubes of endothelial cells increased vascularization of the surrounding cardiac microtissues and also enhanced the inflammatory response. This heart tissue model provides a foundation for further studies on inflammation in the heart and creates opportunities for drug screening and disease modeling.

Cardiovascular diseases are the leading causes of death worldwide, taking an estimated 17 million lives each year. To properly function and pump blood around the body for a lifetime, the heart constantly needs energy. Heart muscle cells, called cardiomyocytes, obtain the supplies of nutrients and oxygen they require through the blood. The vasculature then acts as a barrier between the cardiomyocytes and the blood, selecting the nutrients that enter the heart muscle. Associate Investigator Dr. Valeria Orlova and her group in the team of Professor Christine Mummery created a unique heart tissue model to study these essential vascular barrier functions.

"PhD student Ulgu Arslan developed a cardiac microtissue model using hiPSCs, whereby vascular endothelial cells spontaneously formed in and around these microtissues and linked up with the blood vessel structures they contained through anastomosis [the process through which blood vessels connect to each other]," Mummery said.

The researchers found that a continuous bi-directional flow of fluids increased the density of the vessels formed in the microtissue and also enhanced the formation of “hybrid” vessels, that is vessels that can act as both arteries and veins. This increased vascularization also improved the cardiomyocyte communication, which in turn resulted in an enhanced response to inflammatory triggers. The model is therefore an excellent tool for future studies on how inflammation can affect cardiovascular diseases, for example, during recovery from myocardial infarction.

The vascularized model developed by reNEW Leiden sets the stage for future studies on how different inflammatory cells and drugs might impact the heart and underlying mechanisms of heart disease with a view to developing therapies.
Therapies for many conditions will require the correction of genetic mutations. Within reWRITE, our stem cell biologists are applying novel gene editing and delivery techniques to address conditions, such as muscular dystrophy, immune deficiency, and Parkinson’s disease.

Removing mutations by reWRITING the DMD gene

Making up 40 percent of our body mass, muscle tissue has a diverse range of functions. It is essential for movement and posture and helps regulate metabolism. The muscle wasting disease Duchenne Muscular Dystrophy is caused by mutations in the DMD gene on the X chromosome. The protein that this gene encodes, dystrophin, is responsible for muscle fiber membrane stability. Patients with Duchenne Muscular Dystrophy experience a progressive reduction of dystrophin expression, causing loss of muscle and motor function. By the age of 12, patients are often wheelchair dependent and lose the ability to use their hands and arms. By their mid to late 20s, they are likely to die from respiratory or cardiac failure.

One reason for the resulting failure of the muscles in Duchenne Muscular Dystrophy patients is continuing inflammation that occurs within damaged tissue sites. In healthy muscle tissue, basic functioning stem cells work to restore damaged areas. However, if inflammation persists, the environment becomes less able to support regeneration. Corticosteroids help manage symptoms by reducing inflammation, but can cause side effects including osteoporosis, immunosuppression, hyperglycemia, dyslipidemia, cardiovascular disease, and psychiatric disturbances. A combination of corticosteroids and physiotherapy can slow the decline in muscle function, but is also not a curative option.

A dedicated disease team, under Professor Niels Geijsen from reNEW Leiden, is developing a non-viral gene editing therapy delivery platform that, combined with the genetic engineering technology CRISPR-Cas, aims to block the progression of Duchenne Muscular Dystrophy.

“Our initial aim is to develop our delivery system technology into a local therapy focused on preserving critical arm and hand function. When these patients are about 15-16 years old, they start suffering from severe weakness in their arms. From that moment on, they are unable to control their wheelchair, use a phone or computer, feed themselves, or even scratch their nose,” said Geijsen.

To change this, Professor Frank Staal from reNEW Leiden recently developed a novel gene therapy for SCID in which the patient’s own stem cells are subsequently “repaired” in the lab and transplanted back into the patient. The therapy is currently in a phase 1/2 clinical trial and rewrites the disease-causing mutation in the RAG-1 gene that completely blocks the production of T-lymphocytes.

“In addition to this mutation, there are other possible mutations in the RAG-1 gene. Patients harboring those have some immunity left, yet their clinical picture is often highly complex. These so-called hypomorphic mutations are also more common, affecting approximately 1 in 50,000 people,” Staal said.

A dedicated disease team led by Staal and pediatrician Professor Atsjan Lankester aim to bring gene therapies for these hypomorphic RAG-1 mutations to the clinic. This would provide a real cure for these young patients, independent of finding a suitable stem cell donor.

“Since the start of our disease team, our Australian collaborators at the Murdoch Children’s Research Institute (Elefanty, Ng and Stanley) have generated several hiPSC lines that contain hypomorphic RAG-1 mutations as model systems. We are currently investigating if we can apply the same method used in our ongoing clinical trial to repair these hypomorphic mutations. This method is based on a fully patent protected lentiviral vector and will allow rapid translation to a clinical product, if successful,” Staal added.

In the coming years, the disease team will also explore the potential of newer technologies to further improve the current gene editing strategy. This work will be based on the groundbreaking technology developed by Professor Niels Geijsen at reNEW Leiden. Moreover, they will develop standard regulatory processes in collaboration with reNEW’s PREPARE team that should allow the entry of these therapies into clinical trials. “The efforts should ultimately lead to safe and effective gene therapies for patients with hypomorphic RAG-1 deficiency that are viable in the long term,” Staal concluded.
Navigating stem cell hopes: challenges and mismatches in healthcare communication

The advancement of stem cell research is fostering interest and hope for the treatment or amelioration of disease and illness. The pace of such advancement, however, contrasts with a growing market of clinically unproven stem cell therapies. PREPARE’s PREPARE team addresses the implications of this mismatch for patients and healthcare professionals.

Being diagnosed with a disease or having an experience of illness can trigger feelings of grief, uncertainty, and fear. People’s experiences can vary and be influenced by a variety of factors, such as life situations, disease perceptions, and access to healthcare. In such situations, the regenerative capacity and potential therapeutic benefits of stem cells can foster significant hope. In a broader cultural and political context, it can ignite further hope in a broader cultural and political context.

The internet has become one of the most essential sources for people to obtain health information. But how do they know whether the information about stem cell research and potential treatments found on “Dr. Google” is correct? The PREPARE team held an insightful seminar tackling these important questions.

Is online information about stem cell research trustworthy? Is it understandable? Are touted stem cell treatments even possible? Who wrote and distributed the information found on the web? These are just a few questions that citizens, patients, and healthcare professionals need to tackle when doing online searches to find out about stem cell treatments.

PREPARE, reNEW’s interdisciplinary research team that bridges the gap between research, the clinical, regulatory, and commercial sectors, as well as the general public, hosted a seminar entitled “Rethinking online search for stem cell treatments in an era of ChatGPT” at the University of Copenhagen to explore this. PREPARE theme leader Professor Megan Munsie moderated the seminar, which was organized by PhD student Anders Grundtvig and Professor Klaus Hoeyer from the Copenhagen node, and co-hosted by the European Consortium for Communicating Gene and Cell Therapy Information (EuroGCT).

The audience heard from researchers with expertise in search engines and in how people access health information online, specifically focusing on information about stem cell medicines. As commercially available but unproven “stem cell” treatments have long been marketed online to vulnerable patients, these issues are most pertinent.

Furthermore, as reNEW will be recruiting patients for trials, it will be important to understand how potential participants find information.

Dr. Anna Couturier from the University of Edinburgh focused on the role of artificial intelligence in online health information searches, while Drs. Emma Lane and Cheney Drew from Cardiff University explained how information seeking can influence patient experiences. Grundtvig spoke on the topic “Searching for Stem Cells Treatments: What, Where, and How?”

Associate Professor Anders Kristian Munk from the University of Aalborg then initiated a discussion with the audience. While this is an ongoing challenge, the fruitful discussions contributed to an article on this topic for the journal “Stem Cell Reports.”

PREPARE

Balancing the hope and hype of stem cells within the broader community is critical to manage expectations and reduce misinformation. Research within our global PREPARE team aims to better understand the drivers of societal perception, and specifically address the key challenges faced by our disease teams.
Next generation of talented researchers

A major investment within reNEW has been to train our people in the skills needed to be the best scientists but to also understand the pathway to translation. This will ensure that the next generation of stem cell researchers possess the capability to deliver outcomes.

A record number of PhD and postdoc students from the three reNEW nodes were selected to participate in the annual European Summer School on Stem Cell Biology and Regenerative Medicine. Fifteen enthusiastic young researchers attended the week-long school organized by reNEW Copenhagen’s Professor Kim Bak Jensen on the Greek island of Spetses.

This year’s edition was kicked off by Professor Michele de Luca from the University of Modena and Reggio Emilia, who delivered a lecture on epidermal stem cells. He emphasized the difficulties faced by researchers in bringing their treatments to clinics, especially when it comes to rare conditions.

A lecture on the role of stem cells in neural development was held by Associate Professor Agnete Kirkeby from reNEW Copenhagen, and sought after guidance on the publication of scientific articles and career choices was given by Professor Christine Mummery from reNEW Leiden.

Discussion on ethical and societal issues related to stem cells and a poster session were also held.

The International Society for Stem Cell Research (ISSCR) held its annual meeting in Boston in mid-June. reNEW was well represented with 23 researchers and administrative team members present to network and listen to both talks and poster presentations from reNEW researchers and other stem cell experts.

The event ended with a major recognition of reNEW when Professor Christine Mummery of reNEW Leiden received the ISSCR’s Public Service Award. Colleagues and former colleagues paid tribute to her persistent commitment and hard work on behalf of stem cell research.

The second reNEW Annual Scientific Meeting (ASM) took place at the Pharmakon Conference Center in Hillerød outside Copenhagen in April. Roughly 110 participants gathered, including all the principal investigators (PIs), their key postdocs and PhD students, reNEW administrative staff, most of the members of our Scientific Advisory Committee (SAC) and Scientific Leadership Committee (SLC), as well as the dean of the University of Copenhagen and key representatives of the Novo Nordisk Foundation.

“We have come a long way and had many highlights in just over a year. Ambitions are high. Collaborations are taking off. There is a lot of connectivity between the three nodes within both underpinning and targeted research, as well as on different organs and diseases,” Professor Melissa H. Little said during her welcome speech.

This second ASM offered a strong scientific program with speakers including our PIs, stem cell experts from the SAC, and early career researchers (ECRs). Three days of fully packed sessions with presentations on ongoing collaborative and targeted research, the progress made by reNEW’s six disease teams, as well as the facilities at hand across our three nodes.

“We can do many things to make products translatable [move from discovery to outcome], such as harmonizing data,” Associate Professor Ana Hidalgo-Simon from reNEW’s PREPARE team said.

Social activities were also on the agenda. These included a tough quiz organized by the younger researchers, as well as a guided tour at the nearby castle of Frederiksborg and its baroque garden. Sessions dedicated to research ethics, as well as frank brainstorming on how additional cross-node collaborations could be launched also took place.

“The primary purpose of reNEW is to facilitate collaborations within the nodes to create synergies. So, think big!” Professor Enzo Porrello, reNEW Melbourne’s node director, urged the audience.

“We do many things to make products translatable [move from discovery to outcome], such as harmonizing data,” Associate Professor Ana Hidalgo-Simon from reNEW’s PREPARE team said.
reNEW workshops on translation

One of our key strategic objectives is to deliver translational outcomes from our stem cell and gene research. We aim at accomplishing this by building bridges between researchers and the clinical, regulatory, and commercial sectors. This is easier said than done, which is why our three nodes hold regular workshops on this important goal.

Too often, stem cell or gene therapies will not make it out of research and reach patients due to scientific challenges followed by clinical trial issues, regulatory hurdles, or even a lack of public acceptance. To counter this, reNEW has its own translational ambassador, Associate Professor Ana Hidalgo-Simon, whose goal is to support reNEW's research to reach patients. She comes from the European Medicines Agency (EMA), where she was the head of advanced therapies.

After visits to reNEW Copenhagen and reNEW Melbourne, Hidalgo-Simon introduced researchers to the world of quality standards and good manufacturing practices (GMP) at the Leiden University Medical Center (LUMC), together with Chantal van Litsenburg, LUMC's manager for translational effectiveness, and Dr. Pauline Mei, the head of its Center for Cell and Gene Therapy. She has also held inspiring lectures on the regulatory framework for advanced therapy medicinal products (ATMPs) at our three nodes.

“Knowing and understanding the basic principles of GMP is essential for everyone working in the development of ATMPs irrespective of the phase of development,” Hidalgo-Simon said.

reNEW has also invited guest speakers such as Dr. Heather Main, who shared her own journey in translating a protocol for human pluripotent stem cell-derived retinal pigment epithelia (hPSC-RPE) to the launch of an ATiMP (where the ‘i’ stands for investigational) with the younger researchers within reNEW.

The feedback from the participants in the workshops was positive. “It makes you reflect on your long-term goals and what you are currently working on in the lab,” said one researcher.

Targeted research theme meetings

The strength of reNEW lies in its collaborations across nodes. Each of our targeted research themes has held both online and face-to-face meetings in 2023, enabling open communication, relationship building, learning by example, and the exchange of ideas.

The two reWRITE disease teams held thematic meetings during their visit to reNEW Melbourne in September, where they shared the progress of their research with their respective disease teams. Each team seeks to improve the function of stem cells by editing their genetic information. Currently, their research focuses on developing new therapies for Duchenne Muscular Dystrophy and hypomorphic RAG-1, a rare genetic condition that affects the function of the immune system.

“As soon as people felt more comfortable and knew each other better, the atmosphere in the room changed completely and with it the discussions. This would never have happened during an online meeting,” said Dr. Lisa Ott de Bruin.

The PREPARE team held its inaugural retreat in April, in conjunction with reNEW's Annual Scientific Meeting in Denmark. This retreat was attended by members of PREPARE from all three reNEW nodes.

PREPARE projects have been designed to be complementary and conducted in a culture where collaboration and input from all members is encouraged to maximize productivity and impact of this body of research. To foster this collegiate environment, the PREPARE retreat facilitated introductions and enabled discussions to identify additional collaborative opportunities across this interdisciplinary team.

“By meeting in person, we fully explore how we can leverage our diverse expertise and interests that is just not possible online or via email. These discussions have directly led to co-authored publications, grant applications, and built a momentum that has enlivened our fabulous themes,” PREPARE theme lead, Professor Megan Munsie, said.
Next generation of talented researchers

reNEW Melbourne training

In 2023, reNEW Melbourne provided a number of training opportunities to its researchers. Dr. Hieu Nim attended the Stem Cell Niche meeting in Copenhagen, Dr. Sarah Yue the QUT/MTP Connect Bridge Program and Associate Professor Richard Mills the EMBO Lab Leadership Course. Several junior researchers were also able to participate in the annual European Summer School on Stem Cell Biology and Regenerative Medicine. (See p. 49)

The premier training event, however, was Science Meets Parliament (SMP). This annual event, which is organized by Science Technology Australia, is the country’s most powerful vehicle for deep engagement between the STEM sector and policymakers.

Four members from reNEW Melbourne attended SMP: Drs Adam Piers, Beth Stout, Sara Howden, and Ritika Saxena. The focus was on how to work with parliamentarians, influence decision-makers, and advocate for critical policy changes. During the main event, which took place at Australia’s Parliament House in Canberra, the researchers had the opportunity to network with parliamentarians from across the nation.

“We got to witness how politicians want to do the best for the people they represent and are willing to know more and learn more in order to accurately and responsibly respond to tricky questions from their communities,” Saxena said after meeting up with Kate Chaney, an independent Member of Parliament.

Overall, attending SMP gave Piers, Stout, Howden, and Saxena real-life experience in elevating visibility, awareness, and understanding of stem cell research within the federal parliament and building relationships to bring STEM expertise even more deeply into the service of the nation.

reNEW Copenhagen training

In 2023, reNEW Copenhagen offered training courses, coaching sessions, and seminars to support employees’ professional and personal development around communication, teamwork, innovation, inclusive leadership, parenthood in academia, and business development.

These up-skill initiatives not only provide PhD students and principal investigators with workable insights outside of their specialist academic areas, but they also strengthen group bonds, encouraging networking and cross-lab collaboration.

New this year was the Leadership & Management Skills course, which included training on communication skills, work organization, goal setting, establishing and maintaining collaborations, addressing conflicts confidently, leading with and without being in charge, supervising and mentoring, as well as delegating.

“Overall, attending the course was very useful and provided me with workable insights outside of my specialist area of cell biology,” said Dr. Hieu Nim. “We got a great opportunity not only to learn but also to network with colleagues from other departments.”

More than 40 junior researchers from reNEW Copenhagen attended the event, which took place at Denmark’s Folketing and the Danish Parliament House in Copenhagen. The three-day course resulted in over half of attendees creating a peer group and saying they would recommend this course, reNEW will continue to offer this course every year.

reNEW Leiden training

reNEW offers training opportunities to all its researchers. Early career researchers (ECRs) in particular frequently follow a variety of training courses that allow for their personal and professional development. A good example of this was the very first reNEW Leiden ECR retreat, which took place in September. The junior researchers participated in several scientific and non-scientific activities during the event to meet other reNEW ECRs, foster new collaborations, reflect, and develop new skills.

More than 40 junior researchers from reNEW Leiden attended the retreat in Noordwijk, the Netherlands. The first part of their program was a workshop on inspirational speaking, designed to improve the presentation skills of our researchers. The lessons learned in this workshop were immediately put into practice during the scientific oral and poster presentations that followed at the retreat.

The second part of the program centered around career development. The ECRs discussed the challenges they face as researchers and how to cope with them in discussion tables led by reNEW associate investigators. Afterwards, reNEW alumni shared their career experiences within and outside academia in an interactive discussion.

In between and after the activities, the junior researchers took the opportunity to get to know their reNEW colleagues through fun social activities such as a wet lab Olympics. The retreat was a great event to stimulate new collaborations and initiatives within reNEW Leiden and contributed to the personal development of the attending participants.
Driving international research collaboration

Collaboration and exchange are a critical strategy for reNEW. In 2023, we invested in collaborative activities, resources, exchanges, and platforms of value to all nodes. These investments represent a unique “point of difference” for reNEW, enabling all researchers to grow the next stem cell medicine outcomes.

All reNEW researchers now have access to a 30,000 small molecule library specifically designed, manufactured, and banked for use within reSOLVE for drug development. This library was specifically designed to include readily modifiable compound scaffolds and reduce false positives. During 2023, the reNEW library was synthesized and banked with Compounds Australia, a compound repository supported by the Australian Government as part of the National Collaborative Research Infrastructure Strategy (NCRIS).

Small molecule screening remains challenging in an academic setting due to a lack of access to unencumbered molecules. However, the use of small molecules remains a highly successful approach for the development of new drugs. Compounds Australia provides organizations such as reNEW with logistics and cost-effective sample management during drug discovery. The facility, which is located within the Griffith Institute for Drug Discovery in Brisbane, currently curates more than 1.5 million compounds. These include synthetic small molecules, existing drug libraries, and natural product libraries of pure compounds, as well as fractions and extracts.

Compounds Australia stores and curates the reNEW custom library consisting of 30,000 small molecules on behalf of reNEW. All reNEW nodes are now members of Compounds Australia and hence all principal investigators (PIs) will be able to interact with Compounds Australia directly. The library facilitates unrestricted, high-throughput screening efforts within reNEW according to Melissa H. Little, CEO of reNEW.

“Access to Compounds Australia is another step toward enabling high-content screening of stem cell-derived organotypic models that could lead to the identification of small molecules for future therapies and provide new insights into disease biology,” said Professor Kim Bak Jensen at reNEW Copenhagen.

This collaborative initiative will enable reSOLVE projects across the consortium. Accurate human stem cell-derived models of disease, rather than immortalized lines of less biological relevance, will form the basis of phenotypic screens for hit compounds. The focus of many proof of concept projects within reSOLVE is to develop the capacity to generate sufficient cells and develop sensitive readouts to perform such high content screening. Several groups have already, or plan to commence, screening of large numbers of compounds from this library.

“We have also supported an investigative proteomics project aimed at stratifying this unique library by pathway impact. This research collaboration, involving cell types from all nodes, will represent a completely novel approach. The information generated will further simplify the screening process by enabling a smaller number of selected compounds to be screened,” said Melissa H. Little, CEO of reNEW.
PREPARE enriches outcomes of reNEW disease teams

New biomedical advancements raise ethical concerns that demand proactive analysis alongside scientific progress. The reNEW PREPARE team is at the forefront of this challenge, navigating the ethical, social, and economic risks of translating research in the stem cell field. In order to ensure this research is aligned with our potential product portfolio, reNEW has funded PREPARE researchers to become embedded within our disease teams to help ensure that they successfully deliver practical, patient-acceptable, and economically viable therapies.

How should we navigate the potential risks involved with bringing innovative research from bench to bedside? When can first-in-human (FIH) trials be considered potentially therapeutic? Who should be included in FIH trials of new stem cell or gene therapies? These are some of the questions that researchers in the PREPARE team explore across reNEW’s disease teams. There are, for example, a range of activities underway at our Leiden node.

An important starting point for many of the ethical inquiries is to make an inventory of stakeholder perspectives. Dr. Hilda Mekelenkamp examines stakeholder views on a novel gene therapy for immunodeficiencies within Professor Frank Staal’s disease team. Isabelle Pirson, a PhD candidate, scrutinizes stakeholder perspectives and ethical considerations regarding gene therapy for Duchenne Muscular Dystrophy being developed within Professor Niels Geijsen’s disease team. Pirson is supervised by Professor Martine de Vries, Assistant Professor Nienke de Graeff, and pediatric neurologist Dr. Erik Niks.

In Professor Eelco de Koning’s disease team, PhD candidate Lieke van Kempen assesses stakeholder perspectives and ethical considerations in the development of stem cell therapy for diabetes. Her research delves into the crucial ethical question of who should participate in FIH trials. Should FIH include health controls or only patients? Should enrolled patients have less or more advanced disease? These findings inform recommendations on the boundary between research and care, as well as the inclusion of “vulnerable” populations in FIH trials.

While specifically linked to these current disease teams, insights from this research will inform work being undertaken by PREPARE colleagues at reNEW’s other nodes and provide starting points for further ethical analysis on crucial questions, such as the inclusion of children in FIH studies. Such interdisciplinary and collaborative efforts led by PREPARE contribute to the further responsible development of innovative approaches to cell and gene therapies.
Supporting our themes through collaborative initiatives

With an investment of more than DKK 34 million (EUR 4.6 million) from 2022 to 2026, all our collaborative initiatives support the targeted research opportunities across the nodes.

Within reBUILD, support includes the provision of development advice, access to clinical grade pluripotent stem cell lines, and support for clinical trial sites. The design and construction of a 30,000-compound library for screening provides reSOLVE researchers with a unique freedom to operate.

The embedding of the PREPARE team within reNEW’s major disease teams will assist in negotiating ethical, legal, social, and economic considerations in the process of product development.

reNEW’s global exchanges

In 2023, reNEW supported 22 exchanges between nodes, totaling 332 days. This was in addition to participation in theme and disease team workshops and conferences.

reNEW exchanges support

- Advanced training in new technologies
- Experience within specific research facilities
- Transfer of technologies within and between teams
- Team building, project planning, and transfer of technologies within research collaborations
- Students and postdocs to experience a different research environment

PREPARE projects integrated into all disease teams

Activation of stem cell derivatives

Disease modeling

Drug screening

Cell therapy

Gene correction

Comparative database for stem cell models

30,000 compound library for drug screening

Stratification of compounds into pathways

Access to clinical grade stem cell lines with no commercial ownership

External advice on translating to ATMPs

reNEW translational ambassador on sabbatical from EMA

Leiden-led RAG-1 SCID clinical trial site in Melbourne
Building bridges

The challenge in any partnership, whether existing or potential, is to ensure we build sufficient bridges. Throughout 2023, a major focus has been placed on building bridges between our own researchers spanning all three nodes. Additionally, we have actively established bridges with the community across all three countries.

First came reNEWS, now we have reNEWEConncet

In its inaugural year, reNEWS successfully unveiled its external website, renewscience, alongside the introduction of a monthly internal newsletter named reNEWS. While the global website faces a broad external audience and provides everyone with a door into our research, reNEWS focuses on building understanding and alignment within our reNEW community dispersed across two continents, three countries, and multiple departments.

“Sharing stories, victories, news, and activities across reNEW brings us together as a team and reinforces our vision — to create a new generation of sustainable stem cell-based therapies built on our international collaborative network of excellence,” said reNEW’s CEO, Melissa H. Little.

In 2023, our communication channels took a big leap forward with the introduction of reNEWConnect, a comprehensive internal communication platform. This platform empowers individuals affiliated with reNEW to seamlessly communicate, collaborate, and access all the essential tools, fostering a dynamic environment to maximize the benefits of reNEW.

“reNEWConnect facilitates the sharing and accessing of relevant information, including information on funded projects, exchange, travel and conference information, and an overview of global events such as workshops within reNEW. I’m confident it will significantly contribute to elevating our collaboration to new heights,” Little underlined.

Moreover, the reNEWS concept underwent a revamp. A version of reNEWS designed for our numerous external stakeholders was introduced to keep them abreast of our ongoing progress. Simultaneously, the internal edition, catering to the needs of our staff, continues to be accessible through reNEWConnect.
To celebrate Stem Cell Awareness Day 2023, reNEW held an ARTxSCIENCE competition to raise awareness about the potential of stem cell medicine to transform the lives of people with currently incurable diseases, while demystifying complex concepts and making the science understandable for all. The challenge for the participating reNEW researchers was to produce a fusion of art and science in pictures and words, all based on their ongoing research at reNEW.

"With this competition, we aim to create awareness about stem cell research beyond the scientific community. We hope to create curiosity and foster a deeper understanding of stem cell research by exploring the intersection of art and science," said the CEO of reNEW, Professor Melissa H. Little.

The result was 62 amazing submissions of stunning images explaining the power of stem cell research and how it can impact people with incurable diseases. All stem cell photos in the competition were generated by dedicated scientists from reNEW labs in Copenhagen, Leiden, and Melbourne, showcasing their discoveries. Attached to each photo is a story on what the focus of their research is, how it contributes to advancing scientific knowledge or addresses a specific medical need, and how far along the research is with the goal of ultimately impacting clinical therapies.

The evaluation of the photos was done in two steps. All submissions were first posted as a gallery on reNEW’s global social media platforms over a one-month period, during which the public was encouraged to vote for their favorite submission based on image and text. Twelve submissions then made it to an international jury.

The ARTxSCIENCE submissions had more than 265,000 impressions during the month they were posted on LinkedIn, and a huge number of people voted online before the international jury selected the winner among the 12 finalists.

The overall winner of the ARTxSCIENCE competition was announced on Stem Cell Awareness Day, in honor of this day, with all three reNEW nodes taking part in the celebrations. "This is definitely a wonderful way of raising awareness of our field and we look forward to repeating this competition next year," said Little.

You can still visit the ARTxSCIENCE gallery on renewscience/artxscience and see all the stunning contributions from science combined with artistic expression.

Stem Cell Awareness Day celebrated by reNEW

This worldwide event brings together organizations and individuals across the globe dedicated to realizing the benefits of one of the most groundbreaking fields of our time – stem cell research. The involvement of reNEW’s three nodes was evident on this key day. The primary aim of Stem Cell Awareness Day is, as its name states, to enhance public awareness and comprehension of stem cell research. This day has served as a platform for fostering awareness about the potential of stem cell medicine to transform the lives of people, since its inception in 2008.

This year, reNEW took the opportunity to showcase the importance of stem cell research by illuminating the Panum Tower lying in the midst of the campus of Copenhagen University with the winning picture of its ARTxSCIENCE competition.

Numerous reNEW staff convened in both Leiden and Melbourne for drinks and snacks leading up to the announcement of the winner on October 11. Meanwhile, in Copenhagen, they gathered outside the tower to await the countdown. Their patience bore fruit, as the competition’s winner, Antar Drews, was among them.

The illumination on the tower remained visible until the Copenhagen Culture Night, held two days later, serving as a beacon to spread awareness about the potential of stem cell research.
Building bridges

Winner of reNEW’s ARTxSCIENCE competition shows life in the making

The inaugural reNEW ARTxSCIENCE competition unfolded mid-2023, providing scientists across reNEW with the opportunity to showcase the most captivating snapshots of their groundbreaking research.

The 12 top entries then underwent careful examination by an international jury composed of Professor Brigitte Holst from the Novo Nordisk Foundation, Professor Insoo Huyn, director at the Museum of Science in Boston, Christel Schollaardt, science manager at Museum Boerhaave in Leiden, and Stem Hall, assisting curator at the Science Gallery in Melbourne. The jury not only used its expertise to judge the submissions’ unique expression and effective communication of the science behind them, but also their potential to raise awareness about stem cell research among the general public.

The coveted first prize was awarded to Antar Drews, a PhD fellow from Associate Professor Jan Zylicz’s lab at reNEW Copenhagen for his picture featuring pluripotent stem cell-derived models of the early embryo, termed blastoids.

A blastoid is made up of roughly 200 cells that resemble the human embryo one week after the sperm fertilizes the egg. These stem cell models open new avenues for the study of infertility, as they circumvent the ethical and legal questions associated with experimenting on real human embryos.

“The submission [of the blastoid] captures the intersection between art and science and is a perfect fusion of an extremely beautiful image and an impactful and clearly communicated story that people can understand and relate to. The winner has a great potential to raise awareness about stem cells and how stem cell research can help transform lives,” the jury agreed.

Roughly one in six people globally are affected by infertility, with most unsuccessful pregnancies failing within the first week after conception. As blastoids model the initial stages of human development, such models may help researchers understand the underlying causes of early pregnancy loss.

This beautiful picture not only features as the cover of reNEW’s Annual Report 2023 that you are currently reading. It was also projected onto the 75-meter-high Parum Tower, which is part of the campus of Copenhagen University, to mark the global Stem Cell Awareness Day held on October 11.

Eager students learn about reNEW’s research efforts at UniStem Day

Approximately 800 high school students attended presentations and took part in discussions and lab visits during the UniStem Day held across reNEW’s three nodes in March. The objective of this annual event is to allow research institutes to highlight their stem cell activities to students and arouse their interest.

The UniStem Day has over the years turned into the largest educational outreach initiative on stem cells and regenerative medicine in Europe, with some non-European countries also taking part in this promotion effort. It was the first time that reNEW took part in this event.

“This was a huge success with almost 800 high school students participating globally,” said reNEW’s CEO, Professor Melissa H. Little. And participating students agreed. “I liked that there were different people (presenting, who each had) different perspectives on stem cells. I learned a lot about how many options we have with stem cells, said one.

In Copenhagen, roughly 450 high school students attended lectures on stem cell research, regenerative medicine, success stories from the field, and the ethical aspects stem cell research raises. The set up was similar in Leiden, though a young patient suffering from type 1 diabetes was also present here. She explained how breakthroughs in stem cell research could eventually change her life.

In Melbourne, the students completed five different hands-on activities to experience how our researchers study heart development and heart disease using stem cells, uncover disease causing genes in a computer model of the heart, and unpack the ethics of participating in research. The around 200 students also listened to presentations held by postdoc fellows and reNEW researchers on their stem cell research.

The participants were enthusiastic as they walked out of the event. “I really enjoyed the intersection between the students and scientists, and the different varieties that each scientist contributes to one specific organ. Really enjoyable and informative,” said one student. Another one was more interested in the ethical aspects of stem cell research. UniStem Day “helped me get a good understanding of how ethics are applied to research.”
High school students explore the power of stem cells

Approximately 50 high school students immerse themselves in the world of stem cells during a visit to reNEW Copenhagen. The day kicked off with a warm-up quiz and an engaging lecture about stem cells. Thereafter, one group headed to the lab, while the other delved into the social and ethical aspects of stem cells. In the wet lab, students explored the power of stem cells and how reNEW Copenhagen works with embryonic stem cells, blastoids, tissue stem cells, and organoids. They had the opportunity to sort cells and look through the microscope. Meanwhile, researchers explained their work, emphasizing the relevance of stem cells for disease modeling, future treatments, and how they work toward therapeutic applications. In the dry lab, the students were challenged to discuss the concept of stem cells in round-table sessions: one about the temporality of stem cell development, from idea to product, another on the concept of stem cells, and a third on stem cell information available on the internet.

Without doubt, the day was highly appreciated. "It was fantastic to witness the researchers’ passion as they spoke about their work," one student said. "We look forward to welcoming the next group of students to make it just as big a success!"

reNEW Leiden strengthens its ties with the Leiden Bio Science Park

The Leiden University Medical Center is located in a vibrant life science ecosystem at the Leiden Bio Science Park. To strengthen ties with current and potential collaborators from the science park, reNEW Leiden organized a TechTalk. During the event, our researchers engaged with companies from the science park and presented the techniques used within the consortium.

Four speakers from reNEW Leiden and a guest speaker showcased their work. Dr. Ilse van der Vaart, senior scientist at the reNEW Leiden human induced pluripotent stem cells (hiPSC) hotel, presented the services and activities performed by the facility. "All types of researchers that work at the science park come together. For us, it is a great opportunity to form collaborations and get in touch with these people," she said.

Associate Professor Ana Hidalgo-Simon took the opportunity to stress the importance of collaboration between academia and industry to bring advanced therapy medicinal products to clinics. "During this TechTalk, companies and academics are coming together. I’m hoping that the interactions and questions between these two groups will give everyone food for thought, spark new ideas, and foster collaborations," she said.

Showcasing breakthroughs in stem cell medicine to the public in Sydney

A stem cell photography exhibition featuring 16 early career scientists (ECRs) from reNEW Melbourne opened a public forum organized by the Australasian Society for Stem Cell Research. During this forum, entitled “Stem cells and Organoids: new insights into health and future therapies,” researchers shared their science with the public. The event, hosted by PREPARE’s theme lead, Professor Megan Munsie, was held at the Australian Maritime Museum in Sydney. Two of the five scientists featured came from reNEW Melbourne; Associate Professors Richard Mills and Silvia Velasco. They shared an insight into their research into muscle and brain organoids respectively and how they use their organoids to understand disease and explore new treatment options.

The ECRs who were present spoke about their research as well as their personal journeys into science and biomedical research. "It was an incredibly positive experience to speak with such a diverse audience about our research," said one ECR. "I learned so much about what interests the public about stem cell research and what questions they have. It was a great opportunity to explain my science."

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New cell therapy facility set to boost reNEW’s research

reNEW’s stem cell research will be supported by the world-class facility planned by the Novo Nordisk Foundation. The Cellerator, as this facility is called, will help to translate breakthroughs in cell therapy research into real-world treatments.

“At reNEW, our research into stem cells is driving the development of new stem cell-based treatments to repair or replace specific cells or tissues,” says reNEW’s CEO, Professor Melissa H. Little. “Given our major programs in cell and gene-modified cell therapies, the construction of the Cellerator will be a major opportunity to help move from the laboratory to the clinic. This is currently a major hurdle in the field. As such, the goals of reNEW and the Cellerator align.”

The facility will be located at the Technical University of Denmark (DTU) in Lyngby and is scheduled to be operational from 2027.

Creating jobs and businesses

Our long-term objective is to deliver new therapies based upon stem cells. Critical steps along the way include protection of intellectual property, transition to clinical manufacturing, clinical trial, and commercial partnerships. reNEW has made progress in all these areas during 2023.
Dutch gene therapy trial expands to Australia thanks to reNEW

Researchers from reNEW expanded their on-going gene therapy trial for children living with RAG-1 Deficient Severe Combined Immunodeficiency (RAG-1 SCID) from the Netherlands to Australia. The therapy will provide these children with a working copy of the RAG-1 gene, meaning they will likely be able to build a healthy immune system and live a normal life. The trial is possible thanks to funding of DKK 6.2 million (EUR 800,000) from reNEW.

Children with RAG-1 SCID are extremely vulnerable to infections as they are born without infection-fighting immune cells. Without treatment, most children with this immune disorder, caused by genetic defects, die from infection during their first or second year.

A stem cell transplant from a healthy donor can cure RAG-1 SCID, but most patients lack a suitable donor. Gene therapy is now revolutionizing treatment by offering a life-saving alternative, while avoiding the serious lifelong complications that can arise from stem cell transplants.

In the up-coming trial at reNEW Melbourne’s base, the Murdoch Children’s Research Institute (MCRI), stem cells will be taken from the child’s bone marrow and provided with a healthy copy of their RAG-1 gene in a specialized laboratory at the Leiden University Medical Center (LUMC).

These modified stem cells will then be injected into the child’s bloodstream, where they will become healthy white blood cells that will build a new, functional immune system.

Professor Frank Staal, principal investigator at reNEW Leiden and Professor Aljan Lancaster from LUMC’s Willem-Alexander Children’s Hospital are behind this trial. Staal recently partnered with Associate Professor Rachel Coney, who is a pediatric oncologist and co-leader of the Bone Marrow Transplantation Group at Children’s Hospital in Sweden, who led the preclinical development of the RAG-1 gene, meaning they will likely be able to build a healthy immune system and live a normal life.

The team behind STEM-PD’s development has also published a behind-the-scenes article in Cell Stem Cell describing the various in vitro and in vivo tests conducted on the stem cell product to achieve regulatory approval for transplantation in humans. Such data is in many other trials kept confidential and not made available to the public.

“Releasing such data provides an unusual window into the comprehensive and rigorous testing needed to bring novel stem cell therapies into clinical trials. This is highly valuable information for fellow scientists in the field and has the potential to speed up the clinical development of stem cell therapies for various other diseases,” Kirkeby added.

The team has also received a regulatory approval from the UK authorities, allowing for the inclusion of UK patients in the trial. A total of eight patients will now be incorporated. Should the results of this ongoing clinical trial succeed in demonstrating the safety of the treatment over the course of 15 months, Novo Nordisk – the STEM-PD team’s research partner – intends to proceed with additional trials and product development toward a product launch over the coming years.

Behind the scenes of a novel stem cell therapy for Parkinson’s disease

Current treatments for alleviating the symptoms of Parkinson’s disease involve daily doses of medications. Over time, these tend to lose their effectiveness and lead to severe side effects. To overcome this, reNEW Copenhagen’s Associate Professor Agnete Kirkeby is part of the team that has developed a novel stem cell transplantation product for Parkinson’s, now being tested in clinical trial.

Parkinson’s disease is a neurodegenerative disease characterized by the loss of normal motor control, leading to rigidity, slow movements, tremor, and difficulties walking. The disease affects approximately 1 percent of people above the age of 60 and, with an aging population, its prevalence is on the rise. The motoric symptoms of the disease are caused by the loss of a particular type of dopamine-producing nerve cell in the brain.

After 13 years of preparatory work, the Swedish regulatory authorities approved the start of a phase 1/2a clinical trial of a stem cell transplantation product called STEM-PD in October 2022. Subsequently, in February 2023, the first patient received a dose of 7 million stem cell-derived nerve cells injected into the brain at Skåne University Hospital in Lund. This marks the first testing of a pluripotent stem cell therapy for brain disease in Europe.

“This is an important step toward bringing stem cell therapies for Parkinson’s disease to patients. Such therapies have the potential to reform the way we treat the disease,” said Kirkeby, a principal investigator at both reNEW Copenhagen in Denmark and Lund University in Sweden, who led the preclinical development of the STEM-PD product.

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Enabling precision medicine
The successful translation of research into medical therapies involves more than achieving research excellence. Ensuring success requires active support in the process of moving successful research results to their commercial, clinical, or social application. To this end, many of reNEW’s researchers have already begun to build bridges with commercial and third-party organizations. reNEW welcomes the opportunity to engage with other international and specialist organizations to continue to work toward the development of novel treatments for patients.

reNEW works hand in hand with numerous partner organizations

Protecting our ideas
As translation of our research to outcomes is a key component of reNEW’s Vision, it is important to protect the new findings originating from our three nodes. Our portfolio of inventions, consisting of unpublished provisional filings, is steadily growing. We are currently mapping the potential path to market for each of the inventions mentioned below and exploring which partners could be critical for their successful market introduction.

Methods and compositions for in vitro haematopoiesis and lymphopoiesis

Tissue generation via the modulation of a particular pathway

Enhanced media for stem and progenitor cell culture

Engineered human cardiac tissue (PCT filing)

A method for revealing disease phenotypes for the purposes of compound screening

A method for enrichment of target cells derived from human pluripotent stem cell clusters by density gradient separation

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Celebrating the many faces of reNEW across the globe
Reporting
2023 at a glance

68 projects in reNEW’s research portfolio

39 internal collaborations

38 commercial/industry collaborations

332 days spent by researchers on exchange in another Node

18 external experts engaged to provide guidance and training

1,148,000 impressions on LinkedIn and Twitter

68% increase in members on LinkedIn

76 publications across the center

119 awards received by our PIs

186 engagements and influencing activities

77 people are now employed at reNEW

Gender distribution

263 Male

127 Female

Number of staff

Technical, administrative and other scientific staff

Research assistant

PhD student

Postdoctoral fellow

Associate Professor or similar

Professor

Master’s student

Assistant Professor or similar
## Financial Reporting

### Financial statement

For the year ended December 31, 2023

<table>
<thead>
<tr>
<th>Budget and spending by node (in million DKK)</th>
<th>Budget</th>
<th>Report spending</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUB node Novo Nordisk Foundation allocation</td>
<td>23.5</td>
<td>17.6</td>
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<tr>
<td>UCPH1 node Novo Nordisk Foundation allocation</td>
<td>65.8</td>
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<tr>
<td>LUMC2 node Novo Nordisk Foundation allocation</td>
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<td>73.8</td>
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<tr>
<td>MCRI3 node Novo Nordisk Foundation allocation</td>
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<td>69.7</td>
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<tr>
<td><strong>Total Novo Nordisk Foundation reNEW income</strong></td>
<td><strong>238.1</strong></td>
<td><strong>223.5</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Budget and spending by activity (in million DKK)</th>
<th>Budget</th>
<th>Report spending</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUB and node management salaries</td>
<td>16.8</td>
<td>15.9</td>
</tr>
<tr>
<td>HUB operations</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Collaboration and exchange</td>
<td>15.5</td>
<td>10.8</td>
</tr>
<tr>
<td>Node administrative and research support</td>
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<td>10.0</td>
</tr>
<tr>
<td>Underpinning research</td>
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<td>Targeted research</td>
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<tr>
<td>PREPARE funding</td>
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<td>5.3</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>238.1</strong></td>
<td><strong>223.5</strong></td>
</tr>
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</table>

### Additional expenditure

Covered by other sources*

<table>
<thead>
<tr>
<th>(In million DKK)</th>
<th>Report spending</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCPH1</td>
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<tr>
<td>LUMC2</td>
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</tr>
<tr>
<td>MCRI3</td>
<td>63.0</td>
</tr>
<tr>
<td><strong>Total additional expenditure</strong></td>
<td><strong>181.3</strong></td>
</tr>
</tbody>
</table>

*Includes competitive external grants and institutional commitments.

1. University of Copenhagen
2. Leiden University Medical Center
3. Murdoch Children's Research Institute