Open Discovery Innovation Network

ÓDIN

2020-2023
FUNDED PROJECTS

ÓDIN

UNITES MINDS TO ACCELERATE DRUG DISCOVERY AND IMPROVE DIAGNOSTICS

ODIN breaks down the barriers between industry and academia by supporting precompetitive research in a collaborative, open environment.

This folder gives the reader an overview of the 11 research projects funded in ODIN in the period from 2020 to 2023.

TABLE OF **CONTENTS**

INTRODUCTION BY THE NOVO NORDISK FOUNDATION

OPEN COLLABORATIONS **STRENGTHEN BOTH INDUSTRY AND ACADEMIA**

During its three-year pilot phase from 2020-2023, ODIN successfully established the first Open Innovation in Science (OIS) framework in Denmark. The OIS framework provides a strong foundation for partnerships between academia and industry. OIS is both patent-free and open-source in its nature, and during the last three years the framework has shown to help accelerate research, foster industry-academia collaboration, and ensure widespread access to knowledge for maximum societal and scientific impact.

I am delighted that the ODIN platform will continue for another five years and now also encompass five of Denmark's major universities. The original rational behind ODIN still stands: As the majority of IP used by industry stems from academia, there is an untapped potential for industry and academia to work closer together.

ODIN is a great example of how society can take advantage of projects that combine industry's knowledge and expertise within drug discovery with the strong research conducted in academia.

The increased network of potential academic collaborators will lay the foundation for the development of products and solutions that deliver meaningful benefits to both people and the planet.

During the next five years, the scientific scope has been refined to effectively meet industry needs. ODIN will actively include more international industry participants, and thereby ensure a global perspective and higher impact.

Both companies and academics have gained much from the first funded ODIN projects. Companies have highlighted the importance of the open and inclusive collaborations made possible by the OIS framework, and academics have enjoyed collaborating closely with industry in an open setting without the traditional IP restrictions.

In the Novo Nordisk Foundation, we are therefore eagerly looking forward to both following the developments of the already funded 11 projects but also to see which projects are funded in the continued ODIN.

Mikkel Skovborg
Senior Vice President, Innovation
Novo Nordisk Foundation

THE MODEL FOR **OPEN INNOVATION IN SCIENCE**

BUILDING TRUST IS KEY TO OPEN COLLABORATIONS

It has been wonderful to see how well the ODIN platform and the OIS framework has been embraced by both industry and academia.

I have headed the ODIN platform for the last three years and will continue as the Head of ODIN for the next five years to come. My team has made an effort to help bridge the gap between industry and academia by bringing them together for different matchmaking activities and, not least, in open collaborations.

When we launched ODIN in 2020 everything was new, and we had to form new paths forward with a platform for open collaborations. But the ODIN community continuously provided valuable feedback and suggestions and made it possible for us to tailor the platform to their needs. In my opinion, we succeeded in building the trust necessary for establishing new and fruitful collaborations and spur ideas, which all parties can benefit from. But we only succeeded because of the goodwill from the community and all of their valuable inputs.

ODIN has now expanded to encompass five of the major universities in Denmark and also new international companies, and I am looking forward to developing the ODIN platform even further. The ODIN team will continue to be open for input and direct our efforts to meet the needs of the community in the best possible way.

In this folder, we will give you an overview of the 11 projects funded in the ODIN pilot. Although the scope of the renewed ODIN has been redefined to meet industry needs, I believe that these projects can serve equally as an inspiration for both industry and academia.

Many of the grant holders have developed research platforms that are broadly applicable for downstream purposes within different research areas. The 11 projects are described on the pages in blue shades, and you are welcome to reach out to the grant holders for more information or suggestions for future collaborations.

If you are curious about the industrial take on the projects, I recommend that you take a closer look at the pages marked with yellow, where some of the industry participants share their view on the ODIN platform and its value proposition.

I highly encourage you to take part in our ODIN community.

Marie Louise Conradsen
Head of Open Innovation in Science
Aarhus University

LIST OF FUNDED **PROJECTS** AND **COMPANY STATEMENTS**

- **BALDER** - type 2 Diabetes and mathematical modelling
- **BIOMETSCO** - biomarkers for occult metastases in colon cancer
- Company statement - **omiics**
- **BioPsych** - biomarkers in psychiatric disorders
- Company statement - **omiics**
- Company statement - **Bioneer**
- **CELPPLUS** - better in vivo mimicking in cell culture assay**s**
- **FRIGG** - a human-based model system to recapitulate chronic kidney disease
- Company statement - **Nordic Bioscience**
- Company statement - **AstraZeneca**

- **IMPAD** - the immune response during Parkinson's disease
- **KidDO** - alterations in the pattern of metabolites during chronic kidney disease
- Company statement - **AstraZeneca**
- **MiCO Platform** - Micro brains for modelling neurological disorders
- Company statement - **Novo Nordisk**
- **oLIVER** - fingerprinting blood samples from patients with liver disease
- **P2P CPP** - intracellular drug delivery using cell-penetrating peptides
- **THOR** - searching for the next generation of drugs targeting atherosclerosis
- Company statement - **Novo Nordisk**

BALDER

- TYPE 2 DIABETES
- MATHEMATICAL MODELLING
- SOFTWARE DEVELOPMENT
- GENOMIC DATA INTEGRATION
- DISEASE UNDERSTANDING

TYPE 2 DIABETES AND MATHEMATICAL MODELLING

A better understanding of a disease usually comes from spending years in the lab or with patients. This is also the case for type 2 diabetes. Until now. The BALDER team used already existing data on type 2 diabetes for in silico research.
Genomic research is rapidly producing vast amount of data including links between genomic variation and disease risk. One of the key challenges is to interpret this complex data in a relevant biological context. To do this, researchers must be able to readily integrate this information into their workflow.

The BALDER team has developed a comprehensive software package that enhances research efficiency and deepens the understanding of genomic associations by creating a user-friendly, structured database for genomic information. The software automates the collection and integration of diverse genomic data based on the user's input criteria and it helps the user link genetic variation to a range of different biological processes including biological pathways and protein-drug interactions etc.

In the BALDER project, the software package has been tested on type 2 diabetes, but it can be used on practically any common disease. The BALDER team's software tool is freely accessible for everyone to download and use. This new and advanced tool for bioinformatic analysis and interpretation builds on advanced analytic techniques to ensure that the tool meets high standards of data integrity and research validity.

The software package meets the critical needs of the genomic research community, which is overflowing with data: It provides an integrated and efficient platform for advancing discovery and innovation as researchers can dive into the vast amount of data and explore the association between genes and complex biological traits. Not just for type 2 diabetes as illustrated in the BALDER project, but for any common complex disease that the researchers are interested in.

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ble cumprobc = 0.0;

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 (int t = 0; t < nt; t++) {
hs[t] = Ei(t, t) * r[t][i] + Ei(t,


 (int k = 0; k < nmodels; k++) {
rma::mat C = Bi;
or (int t1 = 0; t1 < nt; t1++) {
 if (models[k][t1] == 1) {
   C(t1, t1) = C(t1, t1) + ww[t1][
 }
```

Excerpt from the c++ code for the multi-trait BLR model

Peter Sørensen
Head of the BALDER project
Senior Scientist at Center for Quantitative Genetics and Genomics, Aarhus University

"I am looking forward to using the software package in new research projects to identify links between genomic information and disease risks. In the BALDER project, we have tested the software on diabetes in close collaboration with Novo Nordisk and Steno Diabetes Center, and in this way, the open project has expanded my research network.

Now that the project has ended, I would like to collaborate with other companies to demonstrate the relevance and efficiency of the software package on other diseases. The open format in ODIN ensures that I can do this without worrying about rights and regulations."

Peter Sørensen on future collaborations after the BALDER project

LEAD PARTNERS IN BALDER:

- **Peter Sørensen,** Senior Scientist, Aarhus University
- **Mads Fuglsang Kjølby** Associate Professor, Aarhus University

- **Novo Nordisk Reserach Center, Oxford**

MORE INFORMATION?
Click here to visit the BALDER website

BIOMETSCO

- COLON CANCER
- OCCULT METASTASIS
- SPATIAL TRANSCIPTOMICS
- EPIGENETICS
- BIOMARKERS

BIOMARKERS FOR OCCULT METASTASES IN **COLON CANCER**

About 1 person out of 20 will develop colon cancer. When the patients are diagnosed, 1 out of 5 patients already has metastases – the cancer cells have spread to other places in the body, making the disease very hard to treat.

The current treatment for early-stage colon cancer involves surgical removal of the primary tumor and some patients also receive adjuvant chemotherapy as a supplement to eradicate potential metastases. The chemotherapy, however, is not very effective although it is associated with significant side effects.

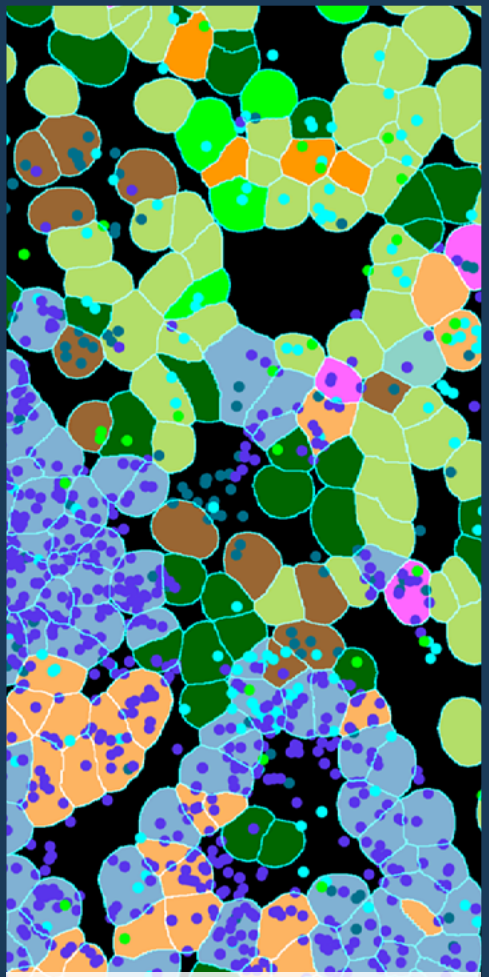
In 2020, the BIOMETSCO project set out to find biomarkers that can help predict whether or not a patient with colorectal cancer also has occult metastases. If present, these small and undetectable metastases pose a significant threat to the patient's survival chances. If not present, metastasis-free patients should not be offered chemotherapy.

So far, the BIOMETSCO project has identified several metastasis-related protein-coding genes and non-coding RNAs through a two-step process:

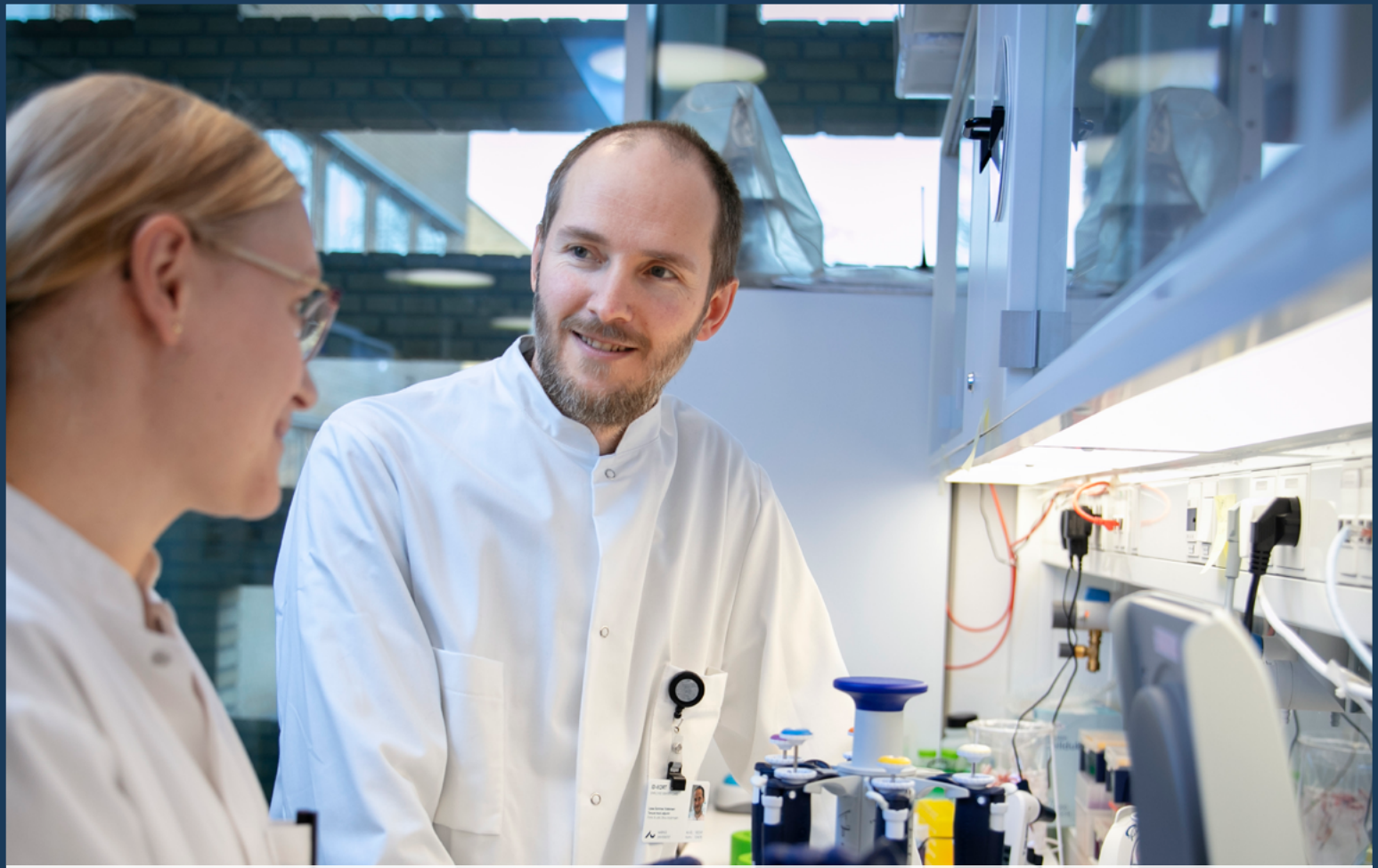
Initially, a comprehensive genome-wide “bulk analysis” was performed to identify genes of interest that were differently expressed between tumors from patients with and without occult metastasis at the time of diagnosis. In addition, tumor tissues were compared to adjacent normal tissues or liver metastasis. Later, the BIOMETSCO team took a closer look at exactly where these differently expressed genes were expressed.
In particular, the BIOMETSCO team to zoomed in on the so-called invasive front of the tumor where cancer cells are budding off from the main tumor mass and believed to be *en route* to metastasize. The team showed that these budding cells express genes related to, for instance, cell motility and migration, and that they are fueled by a crosstalk with certain other cells types in the tumor microenvironment.

The BIOMETSCO team is currently validating the biomarker potential of some of the identified metastasis-related genes in a larger patient cohort and has selected some for further analysis in knockdown experiments. These ongoing experiments aim to clarify whether the cells are still able to metastasize if the genes are non-functional. In this way, the BIOMETSCO team investigates if these biomarkers could also as serve as drug targets for future metastasis-specific treatments in the clinic.

In the fall of 2023, Lasse Sommer Kristensen and Henrik Hager received a grant from the Danish Cancer Society for a follow-up project investigating the diagnostic potential of spatial molecular analyses of the tumor microenvironment.



Spatial transcriptomics analysis of the invasive front of a colon tumor.



Lasse Sommer Kristensen
Head of the BIOMETSCO project
Associate Professor at the Department of Biomedicine, Aarhus University

"It has been a pleasure to openly collaborate with innovative companies both focusing on technological advancements as well as on the development of new bioinformatic tools to enable proper analyses of the vast amounts of data generated by the new technologies."

Lasse Sommer Kristensen on open collaborations with industry

LEAD PARTNERS IN BIOMETSCO

- **Lasse Sommer**
  Associate Professor,
  Aarhus University
- **Henrik Hager**
  Associate Professor,
  Aarhus University Hospital

- **NanoString Technology**
- **BioXpedia**
- **omiics**
- **AstraZeneca**

MORE INFORMATION?
Click here to visit the BIOMETSCO website

omiics

on the value of participating in ODIN projects

"Participating in ODIN is a great opportunity for an SME like omiics in several different ways.

Participation enables us to expand our current knowledgebase in relation to biomarker and drug target discovery.

The resulting publications are a strong channel to document the high value of our service to customers worldwide."

Morten T. Venø,
CTO of omiics

BioPsych

- PSYCHIATRIC DISORDERS
- HUMAN BRAINS
- NON-CODING RNA
- SEX DIFFERENCES
- BIOMARKERS

BIOMARKERS IN **PSYCHIATRIC DISORDERS**

Psychiatric disorders are on the rise. For instance, about 1 in every 5 persons will suffer from depression at some point in their life. But the psychiatric conditions affect not only the patients. Their families suffer mentally from both stress and worry, and the greater society must bear the accompanying economic burden from the health care system and sickness absence from work.

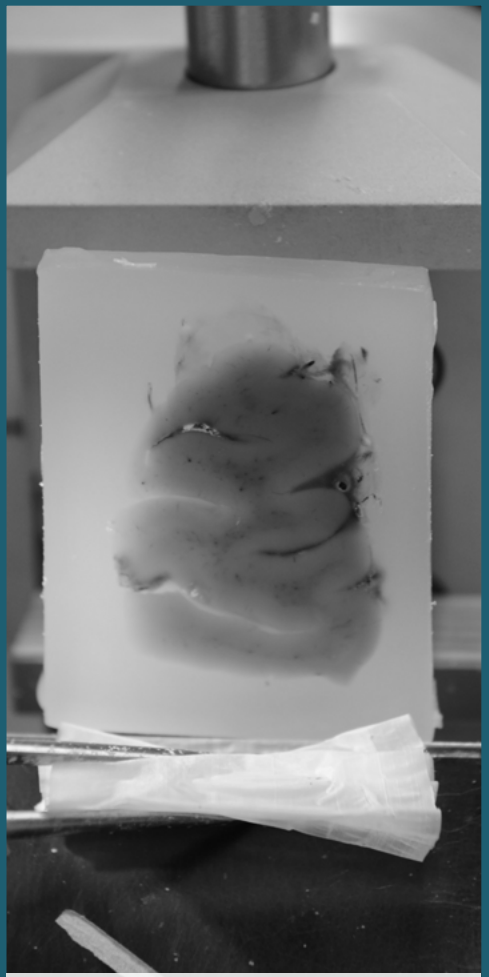
Today, psychiatric patients are diagnosed based on symptoms. This is problematic, because it is difficult to distinguish different psychiatric disorders such as depression, schizophrenia and bipolar disorder due to overlapping symptoms. Therefore, it can also be challenging for health care professionals to diagnose patients and find the appropriate treatment. Even with a clear-cut diagnosis, it is important to choose the best treatment paradigm among several options.

The BioPsych team has isolated small fragments from brains collected from psychiatric patients in Denmark between 1945-1982. These brains, collectively known as the Danish Brain Collection, have not received the

modern treatment we use today. Thus, the biological state of the brains is “natural” and therefore optimal for investigation of biomarkers for different psychiatric disorders.

The goal of the BioPsych project was to gain insight in the underlying molecular mechanisms of psychiatric disorders using human brain tissue. The overall aim was to find biomarkers for different psychiatric disorders that can help diagnose patients and find the most effective individual treatment. The team identified potential biomarkers for different disorders in both men and women. They also succeeded in radiolabeling one of the biomarkers, begetting hope that this could be used to visualize abnormalities in these specific fragments in the brains of psychiatric patients in the future – and potentially develop patient-specific treatments, beneficial for the patients, academic researchers, and the pharma industry.

During the BioPsych project, the team established new collaborations with researchers from both Denmark and abroad. For instance, a collaboration with the Mississippi Brain Bank, which consists of fresh frozen brain tissue samples, will allow the BioPsych team to verify that the identified biomarkers are also found in fresh tissue.
Also, a collaboration with a Danish Professor of clinical neurology will establish whether the biomarkers can be found in blood and saliva samples.



Black and white photo of a paraffin-embeeded human brain sample.

Betina Elfving
Head of the BioPsych project
Associate Professor at the Department of Clinical Medicine, Aarhus University

"It has been a fruitful collaboration with both omiics and Bioneer from day 1 due to the standard agreements in ODIN.

With Bioneer, a platform for microRNA in situ hybridization has been established and we have demonstrated that archival samples from the Danish Brain Collection can be investigated with this advanced high throughput method."

Betina Elfving on open collaboration in ODIN

LEAD PARTNERS IN BioPsych:

- **Betina Elfving,**
  Associate Professor,
  Aarhus University
- **Jørgen Kjems,**
  Professor,
  Aarhus University
- **Lasse S. Kristensen,**
  Associate Professor,
  Aarhus University
- **Dirk Bender,**
  Head of Radiochemistry,
  Aarhus University Hospital

- **Bioneer**
- **omiics**

MORE INFORMATION?
Click here to visit the BioPsych website

omiics

on the company perspective of participating in ODIN projects

"The BioPsych project challenged the limits of what is currently possible with existing methods. That is right where omiics wants to be - pushing tecnological boundaries.

We wanted to participate in the BioPsych project because it was an opportunity to develop an optimal strategy for sequencing of old FFPE samples and thus prove our ability to sequence the most difficult samples."

Susanne Venø,
CEO of omiics

“Bioneer has benefitted from this study by gaining biomarker discovery knowhow by technology implementation and execution of these large cohort studies.

The BioPsych project, included both biomarker discovery and validation and it has been a platform for us in Bioneer to apply new techniques and to take them to the edge of their performance.”

Boye Schanck Nielsen,
Manager at Bioneer

Bioneer

on the value of participating in ODIN projects

CELPPLUS

- CELL CULTURE ASSAYS
- IN VIVO MIMICKING
- NANOTECHNOLOGY
- HIGH-THROUGHPUT DRUG CANDIDATE TESTING
- KERATINOCYTES

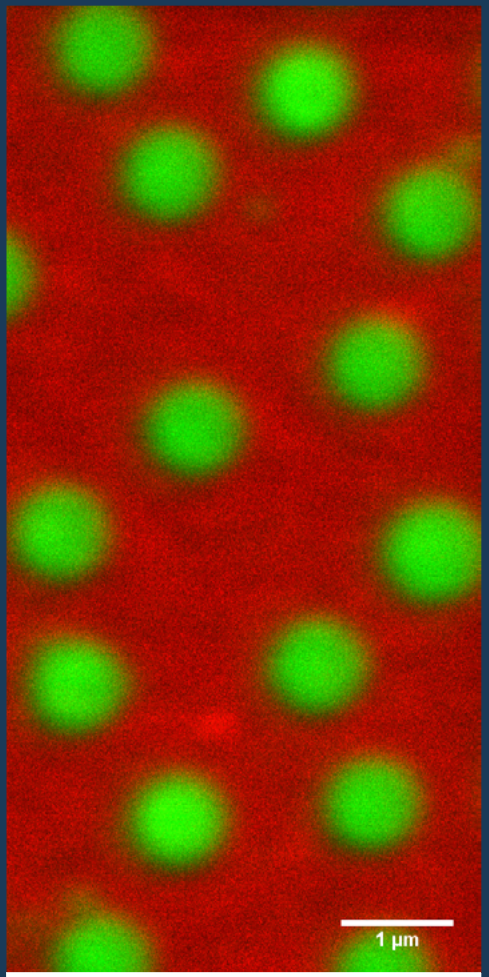
BETTER IN VIVO MIMICKING IN **CELL CULTURE ASSAYS**

Development of new drugs requires good test models. Models that mimic the environment where the drugs are supposed to work. Models that are both safe and easy to use.
Naturally, the best model for human drugs are humans, but there aren't many who would volunteer as models in the early stages of drug development - and it wouldn't be ethical to allow it anyway. This is why cell cultures are a key element in many drug discovery processes.

The problem is that growing in a plastic well is very different from being an integral part of the human body. When developing new drugs for treating skin disorders, for example, skin cells known as keratinocytes are grown in small plastic culture wells as a test model. In the plastic culture wells, the keratinocytes and their response to a potential new drug can be thoroughly investigated in the lab. But the keratinocytes don't behave similarly in the culture wells and the human body. Therefore, care must be taken to help the keratinocyte cell cultures mimic the human body.

The CELPPLUS project focuses on better mimicking of the keratinocytes' natural environment in the small plastic culture wells. The trick is to place proteins into nanopatterns at the bottom of the plastic culture wells. The pattern of specific proteins from the keratinocytes' natural environment ensures that the keratinocytes receive the right physical and biochemical signals that make them behave more similarly to how they would normally behave in the human body. In this way, the CELPPLUS assay provides more relevant results when using cell cultures in the drug discovery process. Ultimately, this can help reduce the high failure rates in clinical and preclinical trials.

The CELPPLUS assay's applicability has been tested on keratinocytes, but the assay can be adapted to fit most types of cell cultures - basically all diseases which can be studied in cell culture wells: If the researchers know, which signals are essential for the cell type to be studied, the protein nanopatterns can be changed accordingly.
Funds have already been raised to ensure that the validation of the CELPPLUS assay can continue during the next three years with a dedicated PhD student. At the same time, the CELPPLUS team will also start looking for opportunities for bringing the assay into closed innovation projects with industrial manufacturers and pharma companies, respectively, to explore commercial applications.



Confocal image of a protein nanopattern (in green) used to verify the quality of the pattern across the 96 well plate.

Duncan Sutherland
Head of the CELPPLUS project
Professor at the Interdisciplinary Nanoscience Center, Aarhus University

"We aim for the CELPPLUS assay to help researchers make better and more relvant results using cell assays.

We hope that the CELPPLUS assay can become a standard assay in both research labs and in the drug discovery pipeline. Therefore, as soon as the last validations are in place, we'll contact both pharma companies and cell culture well manufacturers with an aim to establish closed innovation projects."

Duncan Sutherland on the next steps for the CELPPLUS project

LEAD PARTNERS IN CELPPLUS:

- **Duncan Sutherland,** Professor, Aarhus University
- **Claus Johansen,** Professor, Aarhus University
- **LeoPharma**

MORE INFORMATION?
Click here to visit the CELPPLUS website

FRIGG

- CHRONIC KIDNEY DISEASE
- TRANSLATIONAL RESERACH
- HUMAN-BASED MODELS
- OMICS
- BIOIMAGING

A HUMAN-BASED MODEL SYSTEM TO RECAPITULATE **CHRONIC KIDNEY DISEASE**

The symptoms are non-specific and patients often ignore them because they have other medical conditions that are more pronounced. Therefore, the patients might not pay much attention to the gradual loss of kidney function that causes symptoms such as swollen feet, nausea and itchy skin. But chronic kidney disease, or CKD as it is abbreviated, is a potentially disabling and life-threatening disease affecting about 10% of the global population.

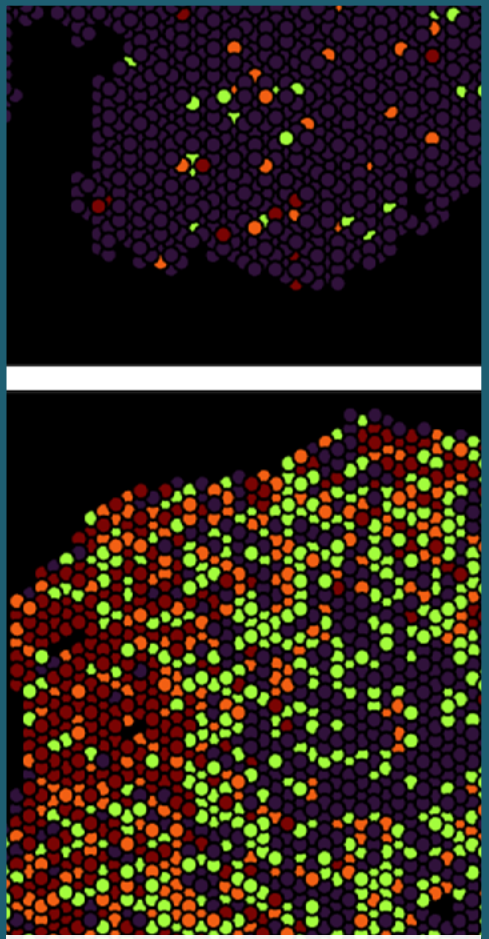
CKD is on the rise and projected to be the 5th leading cause of death in 2040. It is a medical condition where the function of the kidneys gradually decline over time. The incidence and prevalence of CKD is increasing concurrent with the increase in life-style diseases, such as obesity and diabetes. That is why CKD is on the rise.

Currently there is no effective cure for CKD. In animal models, researchers can successfully reduced kidney damage but unfortunately these results do not translate very well to human patients. Therefore, most candidate drugs for CKD fail clinical trials. At the end-stage of CKD,

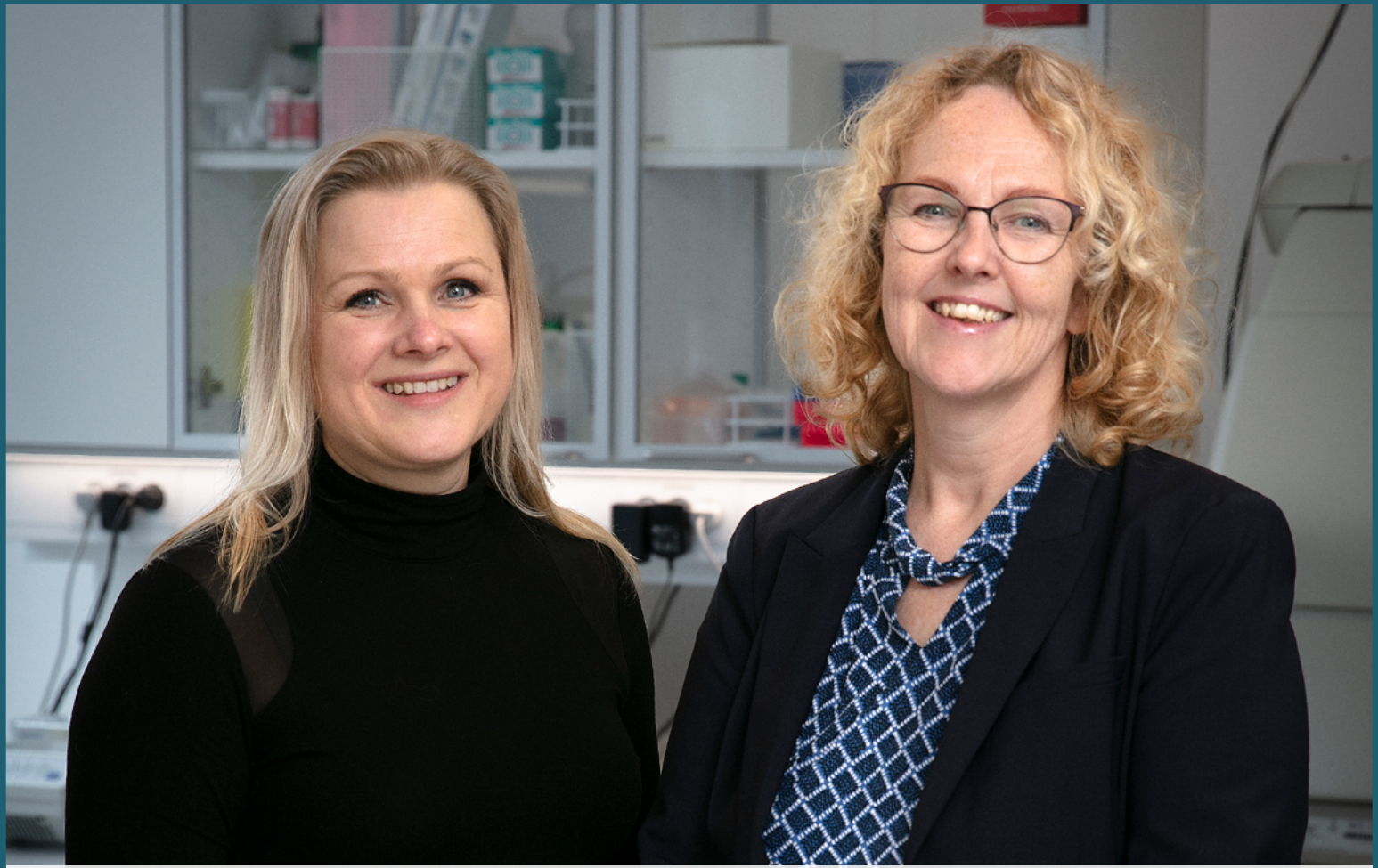
regular dialysis or even kidney transplantation will be necessary for the patient to survive.

In the FRIGG project a large team of researchers developed a human-based model system to recapitulate human CKD. The FRIGG model is based on fresh human kidney tissue obtained directly from the operating theatre. The human tissue is sliced into thin sections in the lab and can be forced into archetypical CKD disease processes to mimic certain stages of human CKD.

With a human model for studying CKD, researchers will get valuable insights into how CKD is initiated and how it progresses over time. Currently there are neither specific biomarkers nor easy methods to monitor the disease progression in patients. The FRIGG model will serve as a platform for identification of potential biomarkers to be used in diagnosis and disease monitoring. The model can also serve as an important step in identifying drug targets and testing potential drug candidates for their ability to reverse or block progression of CKD.



Spatial plot of a human kidney slice from a healthy (top) and CKD patient (bottom) showing collagen1A1 expression.



Lene N. Nejsum & Rikke Nørregaard
Heads of the FRIGG project
Professors at the Department of Clinical Medicine, Aarhus University

"With a human-based model system for CKD at hand, researchers will have a better starting point for identifying potential drug targets.

But more importantly, a human model system will also increase translatability between the laboratory and patients: If we can test drug candidates on fresh human tissue in the lab, there is a higher probability that we see the same effect in patients in the clinic."

Lene N. Nejsum & Rikke Nørregaard
on the purpose of the FRIGG project

LEAD PARTNERS IN FRIGG:

- **Lene Niemann Nejsum,** Professor, Aarhus University
- **Rikke Nørregaard,** Professor, Aarhus University
- **Lin Lin,** Associate Professor, Aarhus University
- **Jørgen Kjems,** Professor, Aarhus University

- **AstraZeneca**
- **Nordic Bioscience**
- **Novo Nordisk**

MORE INFORMATION?
Click here to visit the FRIGG website

Nordic Bioscience

on the company benefits of participating in the FRIGG project

"The ODIN model helps generate new knowledge and it thereby facilitates the development of products that can be commercialized downstream. As an industry partner this is important for us as we now have a new assay in our toolbox that, in combination with the measurements of our biomarkers, we can propose to pharma customers to test their drugs. This fills a void in terms of human preclinical assays that pharma is definitely interested in pursuing."

Federica Genovese,
Director, Cardiovascular and Renal at Nordic Bioscience

"The FRIGG project focused on comparing preclinical and human kidney tissues using cutting edge technologies to identify translatable models.

This research project has given us tools to enable greater understanding of chronic kidney disease pathomechanisms as well as helping improve how we assess new therapies."

Shrikant Mulay,
Director, Cardiovascular, Renal and Metabolism
at AstraZeneca

AstraZeneca

on the value of participating in ODIN projects

IMPAD

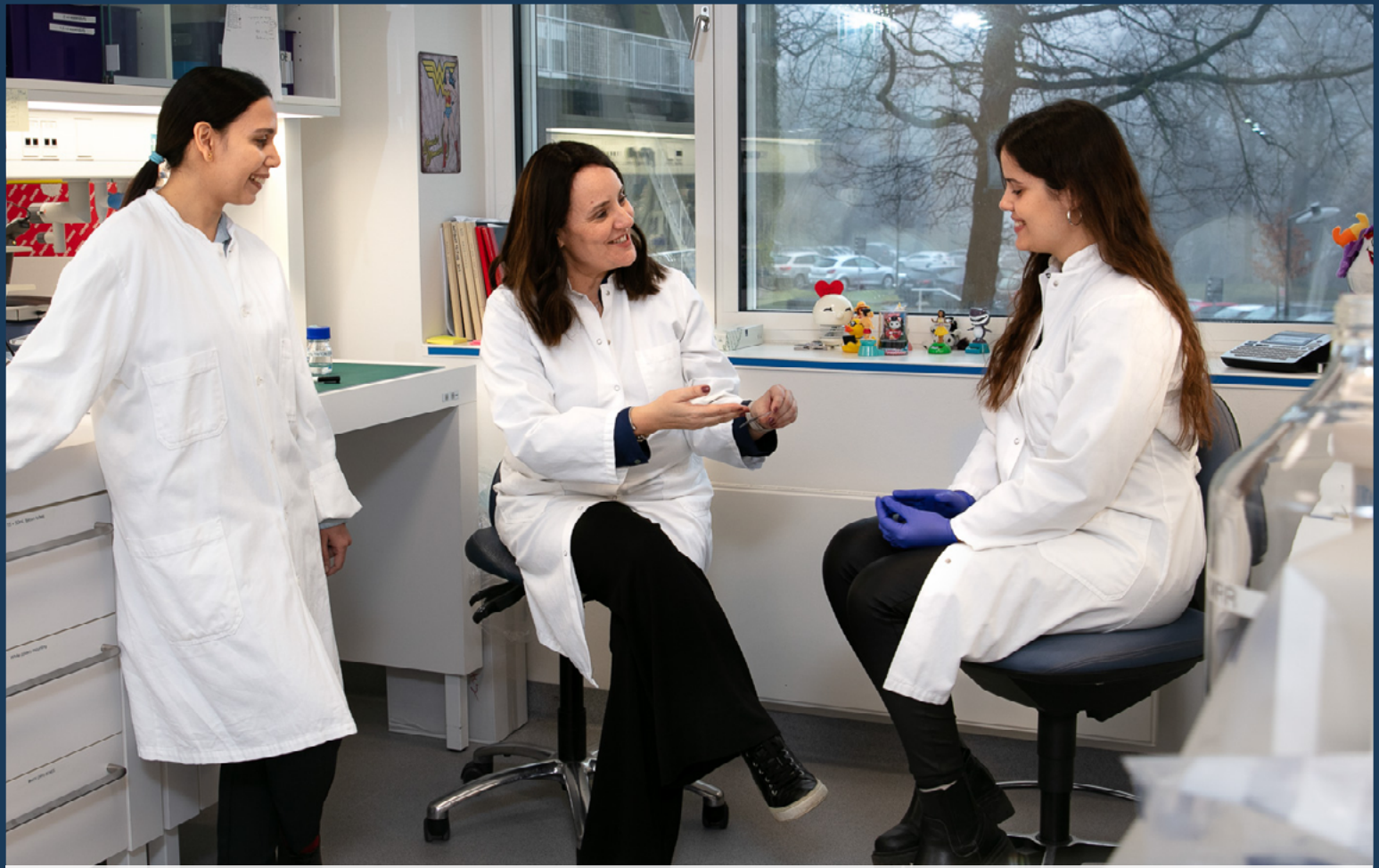
- PARKINSON'S DISEASE
- IMMUNE RESPONSE
- CLINICAL SAMPLES
- MOUSE MODELS

THE IMMUNE RESPONSE DURING **PARKINSON'S DISEASE**

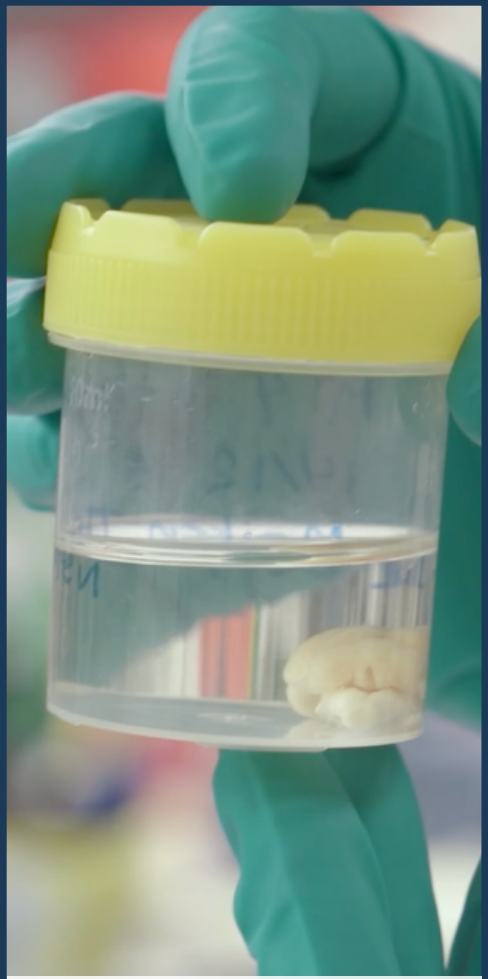
20 million. That's the current estimate for the number of people with Parkinson's disease by 2040. Today, it's the fastest growing degenerative brain disease, but researchers still don't know the full answer to what causes the disease - and they haven't found a cure for the many people with Parkonson's either.

Although there are drugs available for treating the symptoms, they are most efficient at early disease stages of the disease and with time the efficacy of the drugs decreases while the side effects increase. Moreover, these drugs do not stop the disease progression. Therefore, there is an urgent need for novel therapeutic targets that can be used for slowing Parkinson's disease. Moreover, the field lacks relevant disease biomarkers that can be used for patients stratification and follow up.

Studies during the last decade suggest a relevant role for the immune system in the progression of Parkinson's disease. People with Parkinson's show changes on immune cells in brain and blood. However, it is unclear how this evolves during time. It is proposed that the immune



Marina Romero-Ramos, center - with Asst. Professor Ankita Singh, left and postdoc Sara A. Ferreira, right.
Head of the IMPAD project
Professor at the Department of Biomedicine, Aarhus University



Whole mouse brains used in the IMPAD project.

system responds dynamically during the disease stages and these changes can affect neuronal survival. Therefore, changes in blood can be used to monitor disease progression and drugs targeting immune cells might be used to slow down progression.

The IMPAD project focused on just that. First the project aimed to describe biomarkers that can provide information about disease stages and subtypes, which will be valuable in a clinical setting when selecting patients for treatments and also for evaluating the efficacy of potential new drugs. Currently, the assessment of new drugs relies partially on subjective evaluation from clinicians and patients. Secondly, the IMPAD project aimed to identify cells and proteins associated with the neuronal death that might be future therapeutic targets, thus opening new treatments opportunities.

During the IMPAD project, the team used blood samples from both healthy controls and from people with well-characterized Parkinson's disease to identify changes in the immune system at different disease

stages. The team compared these changes in the immune system to neuronal changes and displayed symptoms in patients. In parallel, the IMPAD team evaluated how many of the changes observed in humans are also found in animal and cellular models of Parkinson's. This will determine their translational potential and will inform on whether these models can be used to test novel immunomodulatory targets.

The team is still analyzing the last research data. So far, the results confirm that the immune system is involved in the neurodegenerative processes in Parkinson's disease and that the changes on the immune cells varies between the different disease stages as well as between the sexes and disease subtypes. The initial findings will also ignite new research to investigate whether targeting the cells and proteins highlighted in the IMPAD project might constitute promising avenues in regards to treatment of Parkinson's disease.

LEAD PARTNERS IN IMPAD:

- **Marina Romero-Ramos,** Professor, Aarhus University
- **Jørgen Kjems,** Professor, Aarhus University
- **Per Borghammer,** Clinical Professor, Aarhus University

- **H. Lundbeck**

MORE INFORMATION?
Click here to visit the IMPAD website

KidDO

- CHRONIC KIDNEY DISEASE
- METABOLOMICS
- PROTEOMICS
- HUMAN & MOUSE MODELS
- DATABASE DEVELOPMENT

ALTERATIONS IN THE PATTERN OF METABOLITES DURING **CHRONIC KIDNEY DISEASE**

Chronic kidney disease (CKD) affects 700 million to 1 billion people worldwide. The disease progresses over many months or years and many patients don't show symptoms until major kidney damage has occurred. Therefore, it's important that clinicians can identify those affected at the early stages of the disease and that effective drugs are developed, which can stop progression.

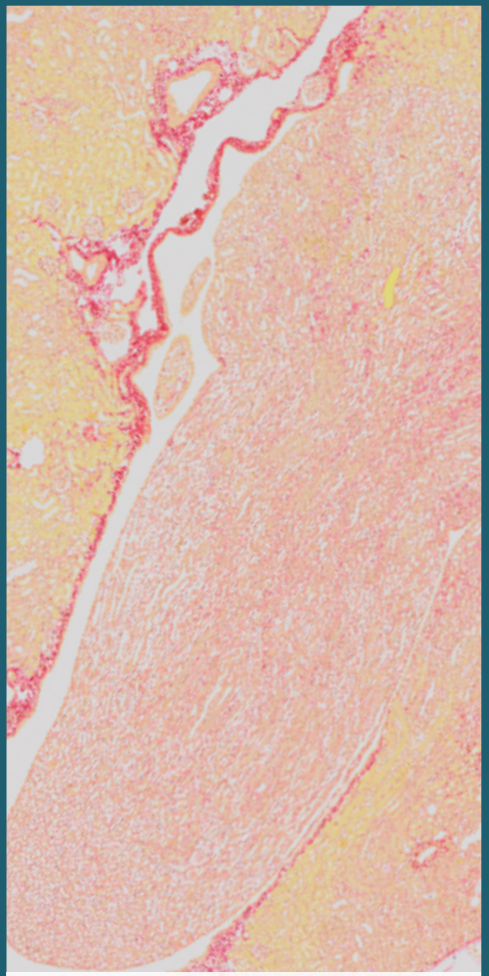
Currently, there is no cure for CKD. At late stages of the disease, the kidney tissue is so damaged that no function resides and dialysis or transplantation is necessary.

The KidDO project was a multidisciplinary project combining expertise within areas such as animal disease models, omics, computer science, and drug delivery. The team's approach for understanding better the basis of CKD to drive treatment strategies forward was to generate a largescale database, which can help researchers integrate metabolomic and proteomic knowledge.

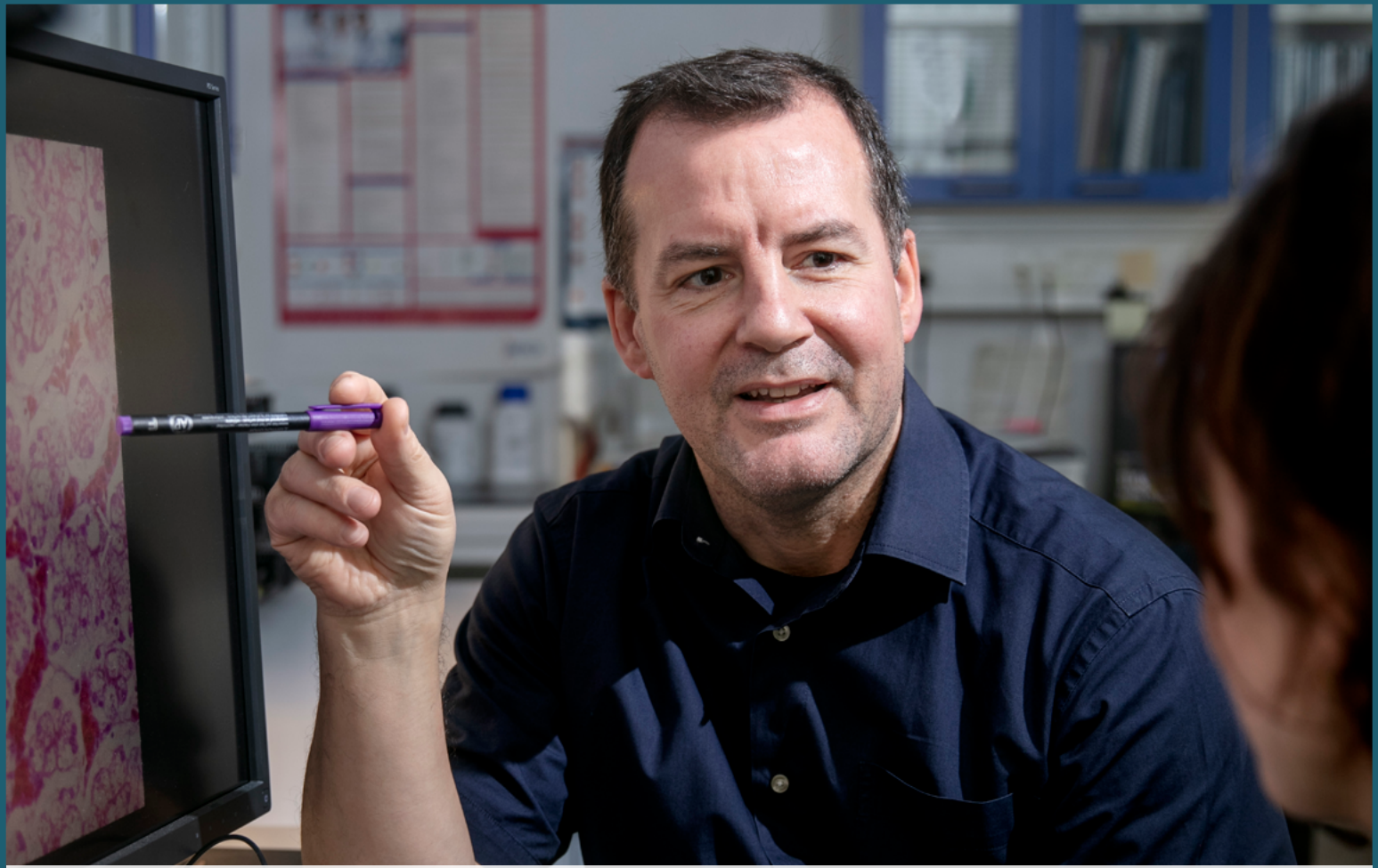
The team's aim was to identify metabolites that can predict progression of CKD and also identify how the interplay between metabolites and proteins within the kidneys drive this progression. Since 2020, the KidDO team has focused on exactly this in both four specifically chosen rodent models as well as in human CKD biopsies. By comparing the data from the rodent models with the data from human biopsies, the KidDO team wanted to help elucidate which animal models can best mimic the human disease. For instance, the team identified a number of metabolites and genes that were universally altered across all models.

The KidDO team has started to create a database that will be fully accessible within the CKD research community, allowing researchers to easily compare data. The idea is that everyone can access all the data and see how things are changing in the diseased kidney relative to healthy kidney tissue.

The KidDO team focused specifically on metabolites, how they change over time in CKD tissue, and how they interact with proteins. The hope is that some of the metabolites may translate to efficient biomarkers, making it possible to identify earlier the onset of the disease and follow progression of CKD in patients using simple urine samples. Furthermore, metabolites also hold great promise for potential therapies. For example, if metabolites regulate disease progression, a cheap and effective treatment strategy could potentially include altering their abundance using specific dietary supplements.



Kidney from mouse model of CKD showing extensive fibrosis (in red)



Robert Fenton
Head of the KiDO project
Professor at the Department of Biomedicine, Aarhus University

"ODIN gave us the opportunity to explore outside of our usual boundaries of research, allowing us to take risks for higher gain we would not usually have the possibility to.

Linking academic researchers with industry opens up new opportunities for collaborative research in kidney disease. The links to industry also provide a direct possibility for pharmaceutical exploitation of novel results"

Robert Fenton on open collaboration within the ODIN network

LEAD PARTNERS IN KidDO:

- **Robert Fenton,** Professor, Aarhus University
- **Ira Assent,** Professor, Aarhus University
- **Markus Rinschen,** Associate Professor, Aarhus University
- **Ken Howeard,** Associate Professor, Aarhus University

- **AstraZeneca**

MORE INFORMATION?
Click here to visit the KidDO website

AstraZeneca

on the the patient value of ODIN collaborations

"When we decided to engage in ODIN it was due to the realization that by working in collaboration, we can stimulate innovation and accelerate scientific discoveries.

In ODIN, we work with scientists from both academia and other companies. This is the key to deliv-er new insights so that we can deliver new treatments for patients"

Pernille Lærkegaard Hansen,
Executive Director and Head of Bioscience at AstraZeneca

MiCO Platform

- NEUROLOGICAL DISORDERS
- HUMAN ORGANOIDS
- MICRO BRAINS
- STEM CELLS
- HIGH-THROUGHPUT DRUG CANDIDATE SCREENING

MICRO BRAINS FOR MODELLING NEUROLOGICAL DISORDERS

Many drugs targeting neurological disorders fail when they reach clinical trials. The drugs are typically evaluated in animal models because they provide the most viable method to test drug candidates in an in vivo setting. However, animal models do not mimic the full complexity of the human brain, leading to the poor translatability of the findings to a human setting. Furthermore, animal studies are also both time consuming and costly to use in a laboratory setting.

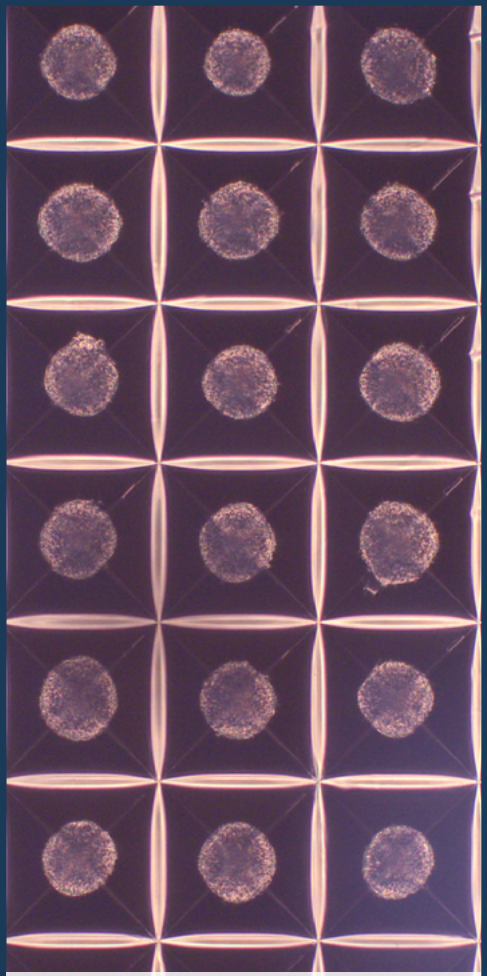
The MiCO Platform consists of miniaturized controlled neuronal organoids, MiCOs, generated from human stem cells. Organoids are complex groups of cells that provide an in vitro model mimicking an organ, and in the MiCO Platform the organoids mimic three discrete regions of the human brain: The fore-, mid- and hindbrain. As such, the organoids are micro brains produced in the lab, which can model e.g., Alzheimer's, Parkinson's, or ALS, respectively.

The MiCO Platform team has developed a protocol for generating micro brains from both healthy and diseased patient samples. In this way,

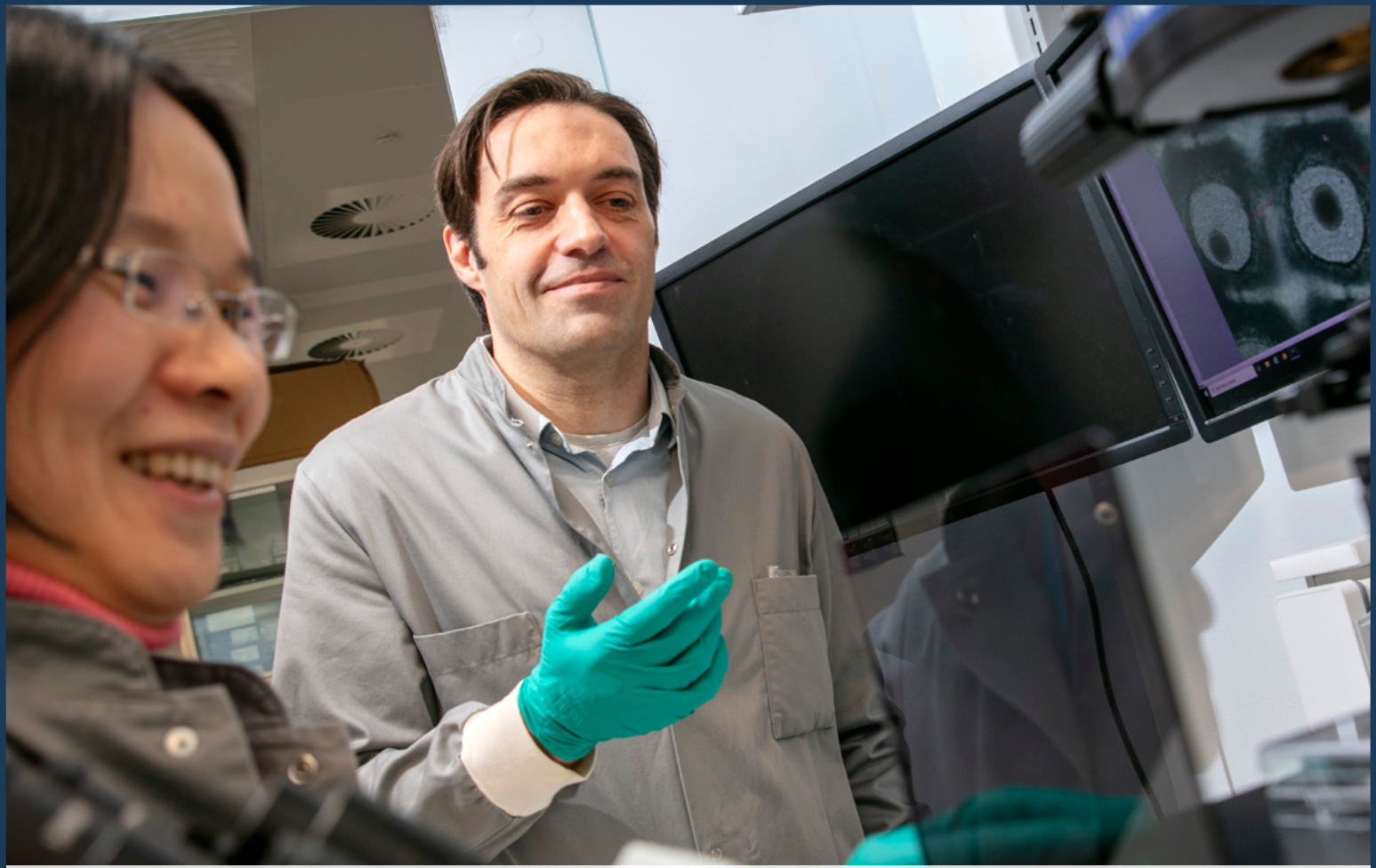
the MiCO platform can be used for both modelling and understanding disease development as well as for drug candidate screening.

The micro brains are fast and easy to produce and, more importantly, they are consistent from batch to batch, thus making it easier to reproduce results. They are also small enough for them to be used in high-throughput screening assays.
Previously, larger organoids known as mini brains have been produced and thoroughly studied in the lab. But the mini brains are two or three times as big as the micro brains, and they are not consistent in size and structure. Therefore,they can't give reproducible results like the micro brains.

The MiCO Platform team hopes that in the future, the platform can be used for both rapid testing of drugs in patient-specific settings and for high-throughput drug candidate screening.
The team is already collaborating with several research groups and is eager to engage in other collaborations too.



Miniaturized controlled neuronal organoids (MiCOs) in culture wells.



Mark Denham, right - with Assistant Professor Muwan Chen, left.
Head of the MiCO Platform project
Associate Professor at the Department of Biomedicine, Aarhus University

"Platform development is rarely funded by public research councils. But ODIN funded the MiCO Platform.

We have developed miniaturized controlled neural organoids, known as MiCOs, from human stem cells. These micro brains provide a fast and easily reproducible method for screening drug candidates in an in vitro human setting that accurately mimics the human brain.

We hope that the MiCO platform can be used as an alternative to animal models in the pre-clinical screening of drugs."

Mark Denham on the output of the MiCO Platform project

LEAD PARTNERS IN MiCO Platform:

- **Mark Denham,** Associate Professor, Aarhus University
- **Daniel Otzen,** Professor, Aarhus University

- **Novo Nordisk**
- **omiics**

MORE INFORMATION?
Click here to vsit the MiCO Platform website

Novo Nordisk

on how the company benefits of participating in the MicCO Platform project

"The MiCO platform project allowed us to study and probe our emerging stem cell therapies as well as our traditional pharmacological compounds at a greater detail.

The platform also enables us to test drugs in a human in vitro model and thus ultimately reduce the amount of time, costs and animals used in our projects."

Jonathan Niclis,
Principal Scientist and Project Leader at Novo Nordisk

oLIVER

- LIVER DISEASE
- RNA BIOSENSORS
- BLOOD SAMPLES
- BIOMARKERS
- DRUG TARGETS

FINGERPRINTING BLOOD SAMPLES FROM PATIENTS WITH **LIVER DISEASE**

Up to 30% of the world's population suffers from non-alcoholic fatty liver disease. The clinical term is metabolic dysfunction-associated steatotic liver disease, or MASLD in short, and it is characterized by a build-up of fat in the liver. Although it is not dangerous per se, it can develop into severe conditions such as MASH, metabolic dysfunction-associated steatohepatitis, which progesses extremely fast and is challenging to identify. In both MASLD and MASH the liver tissue becomes inflamed. Over time, the liver becomes permanently scarred leading to reduced liver function and increased risk of liver cancer, ultimately requiring liver transplantation.

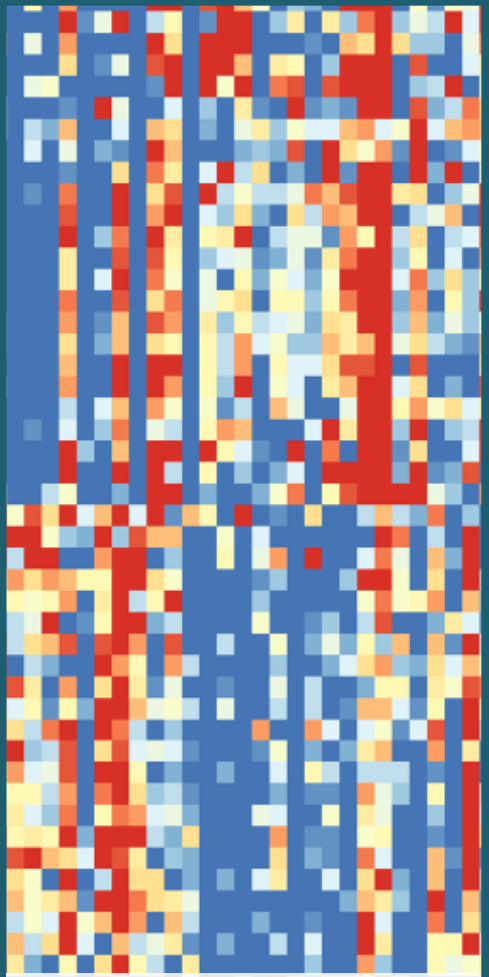
MASH often develops due to a metabolic disorders like diabetes or due to obesity, which entails an increasing number of MASH patients. An unambiguous diagnosis can only be given after a liver biopsy. Therefore, the unmeet need for clinicians are blood biomarkers that can help them accurately diagnose patients.
Using a new approach called APTASHAPE, the oLIVER project uses billions of different small RNA biosensors to generate digital "pictures" of

blood plasma samples. The biosensors that bind proteins in the sample can be identified and quantified using modern sequencing techniques. The result is a sample-specific fingerprint-like pictures that can be used to identify disease and disease status. In the oLIVER project, the team identified discrete "fingerprints" relevant to diagnosis and prognosis of both MASLD and MASH.

The composition of plasma samples can now be readily compared between healthy individuals and MASH patients simply by comparing the pictures. Because the composition of a person's blood indicates the state of health, the sample "pictures" can help clinicians assess how different diseases affect patients. It can also help assess if treatments 'pushes' the composition back to a healthy state.

If an additional step is added where the biosensors are used to 'fish out' their bound proteins, the APTASHAPE approach can be used to identify potential protein biomarkers. Relevant biomarkers may not only be used for diagnostic purposes. In some cases, they can also predict disease development, be used to monitor treatment responses, and indicate new treatment targets.

In a future collaboration with Novo Nordisk, the oLIVER team plans to investigate if (and how) the small RNA biosensor can also be used in the treatment of MASH. Furthermore, the findings from the oLIVER project has given rise to plans about a spin-out company with the aim to further distribute the method in the Danish healthcare system.



"Fingerprint picture": Signals from RNA biosensors that reflect protein changes in the blood of MASH patients.

Jørgen Kjems
Head of the oLIVER project
Professor at iNANO the Department of Molecular Biology and Genetics, Aarhus University

"It has been a pleasure working with companies without first going through the standard legal tug-of-war. I definitely believe that the ability to talk openly and build on each others' ideas have created a space where research is significantly accelerated. This is the background for the oLIVER project's success."

Jørgen Kjems on open collaborations in ODIN

LEAD PARTNERS IN oLIVER:

- **Jørgen Kjems,**
  Professor,
  Aarhus University
- **Christian B. Vægter,**
  Associate Professor,
  Aarhus University
- **Henning Grønbæk,**
  Clinical Professor,
  Aarhus University Hospital

- **Novo Nordisk**

MORE INFORMATION?
Click here to visit the oLIVER website

P2P CPP

- CELL PENETRATING PEPTIDES
- DRUG DELIVERY
- INTRACELLULAR TRAGETS
- ELECTROPHYSIOLOGY
- VASODILATION ASSAYS

INTRACELLULAR DRUG DELIVERY USING **CELL-PENETRATING PEPTIDES**

Most of the proteins in our bodies are currently out of reach for several types of drugs because they are found inside our cells. Each cell is protected by a cell membrane, which carefully guards what enters the cells. At present, however, we have no effective way of reaching drug targets inside the cells with e.g. biologics .

Cell penetrating peptides, or CPPs, hold great potential for delivery of drugs to intracellular targets. Several CPP-drugs are currently in clinical trials, but none have so far been approved for clinical use due to the insufficient safety profile of CPP-drugs . Until now the mechanisms of toxicity have been poorly understood, but the P2P CPP project set out to gain a more in-depth understanding of how CPP-drugs affect the human physiology. The project's overall aim was that and increased understanding could help pave the way for CPP-drugs.

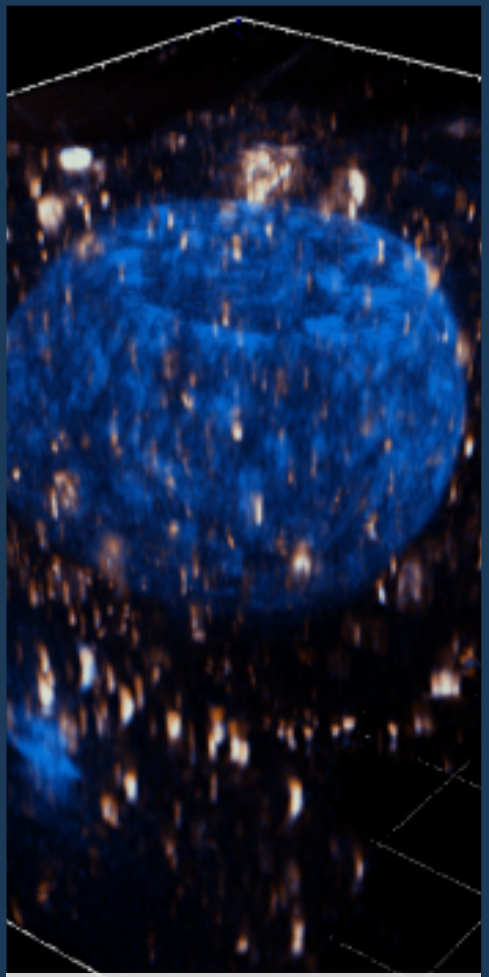
The P2P CPP team used an iterative approach to test different CPP-drugs in both in vitro electrophysiological and vasodilation assays in the lab, before the assay results were compared to the in vivo effect in mice.

So far, the results have indicated that the toxicity of the CPP-drugs are closely related to the drug, which the CPP carries. The toxicity itself is a combination of both anaphylactic shock and depolarization effects in the heart.

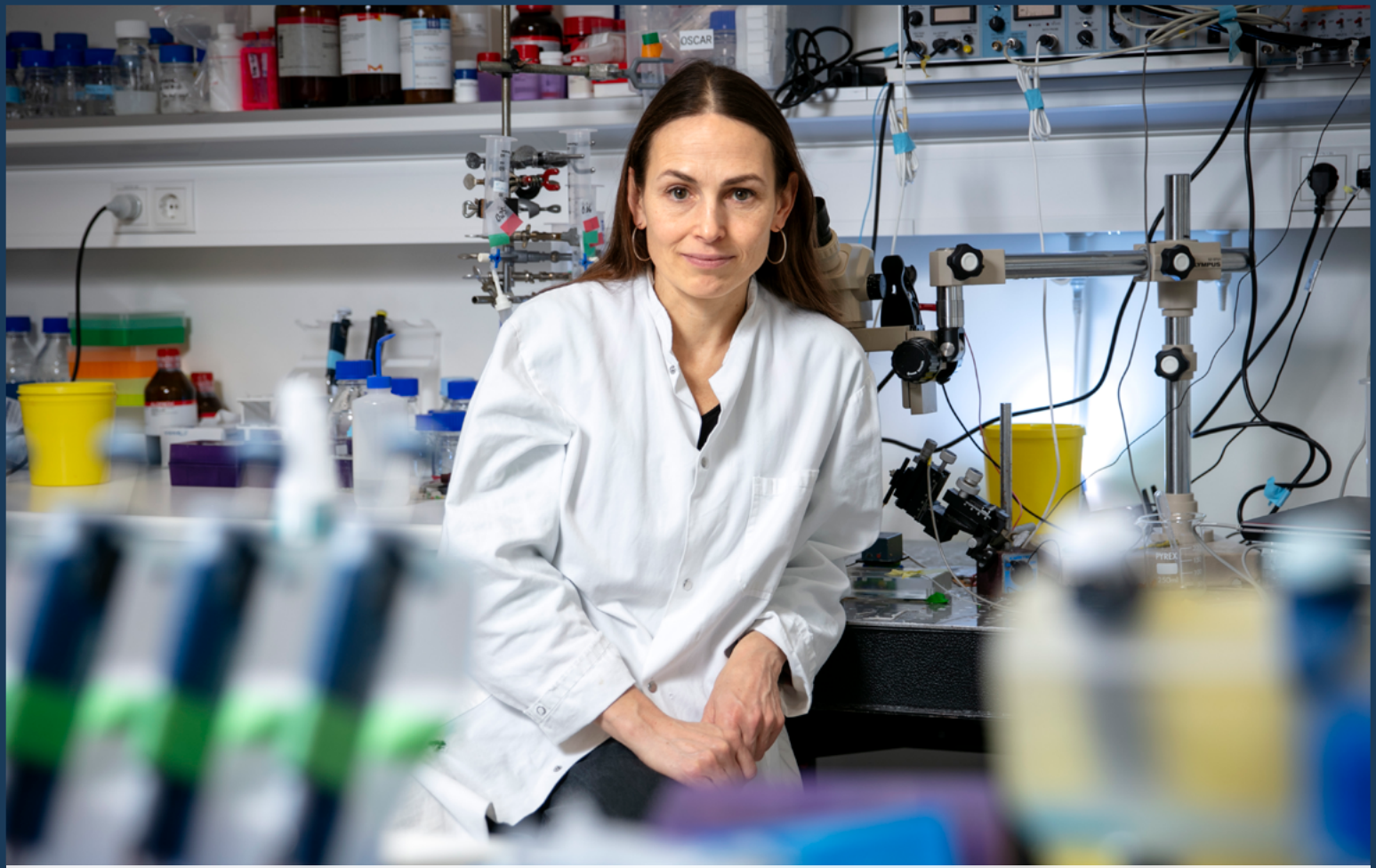
The anaphylactic shock can be avoided by treatment with antihistamine, whereas the cardiac effects are more complex to address. Current studies suggest that CPPs are well tolerated if the cardiac depolarization is prevented by lowering the concentration of the CPP-drug or by opting for a different administration strategy such as slower infusion or a different route.

The P2P CPP project's results have contributed to an increased understanding of the toxic mechanisms of CPP-drugs. Future experiments will help clarify how researchers can best predict which combinations of CPPs and drugs are safe and efficient in intracellular drug targeting. The combination of electrophysiological and vasodilation assays seems to be a promising strategy for predicting potential toxicity of CPP-drugs.

The first two manuscripts are in preparation, and the collaboration has spurred novel ideas, both for implementations in the respective laboratories, and for continued collaborations with both Stipe Therapeutics and pharmaceutical companies with interests in therapeutic peptides.



3D reconstruction of a cell treated with labelled cell pepetrating peptide (in white). Cell nucleus in blue.



Hanne Poulsen
Head of the P2P CPP project
Associate Professor at the Department of Molecular Biology and Genetics, Aarhus University

"It has been quite obvious to do the P2P CPP project as an open collaboration, since the STipe Therapeutics' interest is in the specific mechanism of action of their active compounds and target - not the technical aspects of how these compounds achieve it.
Our basic scientific curiosity, on the other hand, is in the wondrous molecular and physiological mechanisms of cell-penetrating peptides."

Hanne Poulsen on the open collaboration in the P2P CPP project

LEAD PARTNERS IN P2P CPP:

- **Hanne Poulsen,** Associate Professor, Aarhus University
- **Ulf Simonsen,** Professor, Aarhus University
- **Daniel Otzen,** Professor, Aarhus University

- **STipe Therapeutics**

MORE INFORMATION
Click here to visit the P2P CPP website

THOR

- ATHEROSCLEROSIS
- SMOOTH MUSCLE CELLS
- GENETIC AND FUNCTIONAL STUDIES
- DRUG TARGETS

SEARCHING FOR THE NEXT GENERATION OF DRUGS TARGETING **ATHEROSCLEROSIS**

Atherosclerotic cardiovascular disease is a leading cause of death and disability in the world today - and the scope of the health problem continues to increase globally.

The disease is characterized by the development of plaques, which are lumps of cells, necrotic debris, and calcifications that form in the inner lining of arteries. Plaques develop slowly but may suddenly rupture and form life-threatening blood clots that stop blood flow in arteries to the heart or brain.

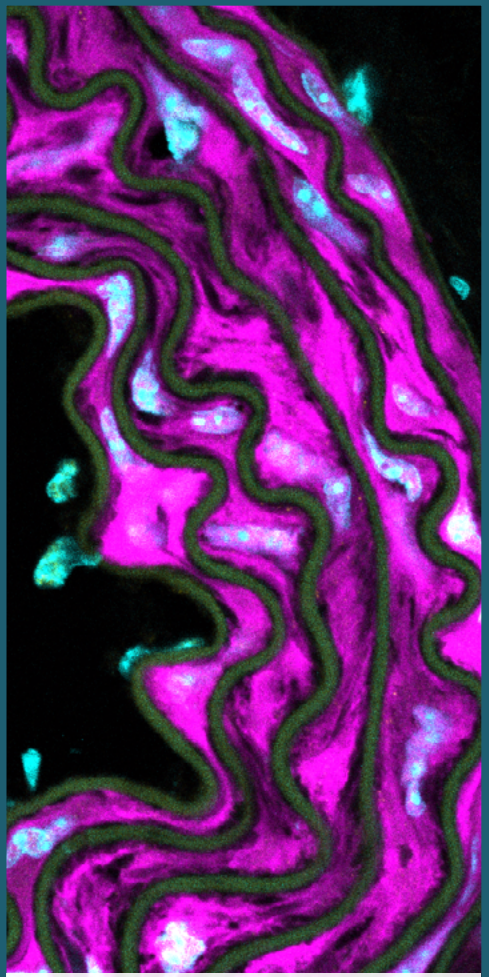
Current drugs target the risk factors for developing the disease, but for many patients it is insufficient to halt disease progression. There is, therefore, a high demand for new effective therapies targeting disease mechanisms within the arterial wall.

The THOR project aimed to find new drug targets to treat atherosclerosis. Because smooth muscle cells play a central role in development of the

disease, the THOR team set out to identify the best drug targets in these cells. Their approach combined human genetics studies with functional studies on smooth muscle cells in the lab.

The THOR project started with an analysis of open data from human genetic databases. After a thorough selection process, a set of candidate genes was identified. These genes are expressed in smooth muscle cells and genetically linked to human atherosclerosis. The function of each of these genes was analyzed in human smooth muscle cell assays designed to showcase the different functions of smooth muscle cells in atherosclerotic plaques. This analysis led to the identification of several pathways regulated by the candidate genes. The THOR team's findings indicate that genetic regulation of these specific pathways can modulate smooth muscle cell function and thereby impact the development of atherosclerosis. Both the set of candidate genes and the pathways they regulate are therefore interesting targets for drug therapy.

The THOR team is continuing the collaboration in a closed project setting to further examine some of the identified drug targets.



Fluorescence microscopy image of a mouse aorta.

Jacob Fog Bentzon, center - with Asst. Prof. Julián Albarrán-Juárez, left and lab tech. Lisa Maria Røge, right
Head of the THOR project
Professor at the Department of Clinical Medicine, Aarhus University

"The ODIN model combines the best of two worlds: the freedom of research and data sharing of the academic world and the strategic focus and application-oriented approach of the commercial world. It is a strong mix."

Jacob Fog Bentzon on the ODIN model

LEAD PARTNERS IN THOR:

- **Jacob Fog Bentzon,** Professor, Aarhus University
- **Mette Nyegaard,** Professor, Aalborg University
- **Novo Nordisk**

MORE INFORMATION?
Click here to visit the THOR website

Novo Nordisk

on how the ODIN platform can help target complex research challenges

"Unravelling the role of smooth muscle cells in atherosclerosis and how to target these cells is not a one-man job.

Here, a team of dynamic, interactive, innovative, and interdisciplinary members are truly needed to fully disclose the complex mechanisms at play – and a platform for this is indeed provided in the open innovation setting of ODIN."

Michael Nyberg,
Scientific Lead at Novo Nordisk

ÓDIN OPEN DISCOVERY INNOVATION NETWORK

A Novo Nordisk Foundation Sponsored Initiative

Photo credit: All full-page photos - Lars Kruse
Research photos - the individual research teams