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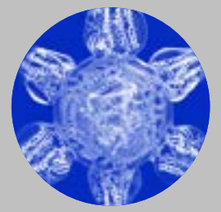
UMCG

Annual Report 2024

ERIBA



Contents

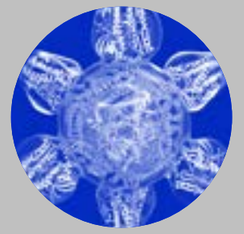
Annual Report 2024

ERIBA
European Research Institute for the Biology of Ageing

1. Foreword by the Director

It is a great pleasure to present to you the Annual Report 2024 of the European Research Institute for the Biology of Ageing. We are proud to share with you our achievements, and the progress that has been made in 2024. Also in 2024 all ERIBIANS have contributed to notable publications, advanced education and several outreach activities to inform the general public.

At ERIBA, we keep marching forward to elucidate the mechanisms that drive ageing, with a view to develop strategies to combat unhealthy ageing and age-related diseases. We published a record number of 66 papers in 2024 showing our commitment to ageing research. These publications were the result of important scientific collaborations within ERIBA, with colleagues from the UMCG and with laboratories around the world . We thank all of our colleagues for this continuous collaboration. Looking forward to the future, we anticipate continuing and expanding our collaborations aimed at the advancement of ageing research.



We are committed to talent development in the field of ageing research. In 2024 excellent PhD students, undergraduates, and postdocs joined the institute and others left the institute to embark on future endeavours. It is great to see that numerous students have a keen interest in ageing research, and they carry out rotations in our institute.

In 2024, our scientists were once again successful in the acquisition of research funding, which includes prestigious and competitive national and global grants. Our scientists have also collaborated with biotech companies, leading to financed collaborative research projects in public-private partnerships. These collaborations have led to finding solutions for age-related diseases and such collaborations also show our commitment to prevention, delay, or reversal of the ageing process.

Knowledge sharing with society is of utmost importance, and I am delighted to share that our scientists were involved in many of the outreach activities. We hosted many outreach events for high school students and the public. Our presence on social media is also one of the many outreach efforts important for sharing our knowledge and findings with society.

Since 2024, ERIBA is part of a new cluster within the UMCG organization. This new cluster Biomedical Science & Technology is aimed at fostering collaborations, nurturing talents to showcase, achieve our ambition to become a global leading ageing institute for innovative research. I greatly appreciate the efforts and contributions of all the staff involved in paving the way for creating a global, highly reputed ageing institute with state of art facilities. I wish everybody all the best for future endeavours.

Folkert Kuipers

2. Ageing Research at ERIBA

ERIBA, a renowned European research center, specializes in the study of ageing. The institute delves into fundamental biology to uncover the underlying causes of ageing. Research at ERIBA is dedicated to understanding the mechanisms that lead to cell loss and the deterioration of function in aged cells and tissues.

Stem cell regulation and mechanisms of regeneration

Eugene Berezikov

Introduction

Resilience is the capacity of a complex system to recover from perturbations. In essence, ageing and age-related diseases are manifestations of the failing resilience of a living organism in the face of various intrinsic and extrinsic stresses. Some animal species evolved better resilience mechanisms than others, and investigating these mechanisms will broaden our understanding of the underlying fundamental biology and can eventually contribute to developing novel therapies in humans.

To this end, we study the model organism *Macrostomum lignano* – a flatworm that can regenerate its body, is long-lived and highly resistant to various stresses, including ionizing and UV radiation. To translate our findings in flatworms to other model organisms, we also utilize the nematode *C. elegans* and one of the shortest-living vertebrate models, the killifish *Nothobranchius furzerii*.

Stem cell regulation and mechanisms of regeneration

Eugene Berezikov

Research Focus

The flatworm *Macrostomum lignano* has an impressively advanced resilience, far beyond other animals (Fig. 1). Besides regeneration, it can also de-grow in the absence of food and survive long periods of starvation, and grow back when food becomes available again. It can live several years, and its mortality hazard does not increase with age. It sustains very high doses of ionizing radiation (120 Gy), as well as sterilization-level doses of ultraviolet C (100 mJ/cm2). We think that all these remarkable resilience properties of *M. lignano* are conferred primarily at the level of the stem cells (neoblasts), because as long as the neoblasts are functional, the damaged cells can be continuously replaced.

In order to start understanding the remarkable biology of this animal, in recent years we focused on developing a genetic toolbox for *M. lignano*. We identified stem cell and germline transcriptional signatures, sequenced, assembled and annotated the genome, and establishing a robust transgenesis method. Importantly, *M. lignano* is the only flatworm species in which transgenesis is available, and it allowed us to generate the first-ever stem-cell-specific *M. lignano* transgenic lines, which opens up tremendous research opportunities. Furthermore, we demonstrated that for its size the animal is remarkably long-lived (more than 2 years), and appears resilient to aging via active regulation of the stem cells. Next to *M. lignano*, we also use other *Macrostomum* species and an acoel *Symsagittifera roscoffensis* for comparative studies of stem cell regulation.

Stem cell regulation and mechanisms of regeneration

Eugene Berezikov

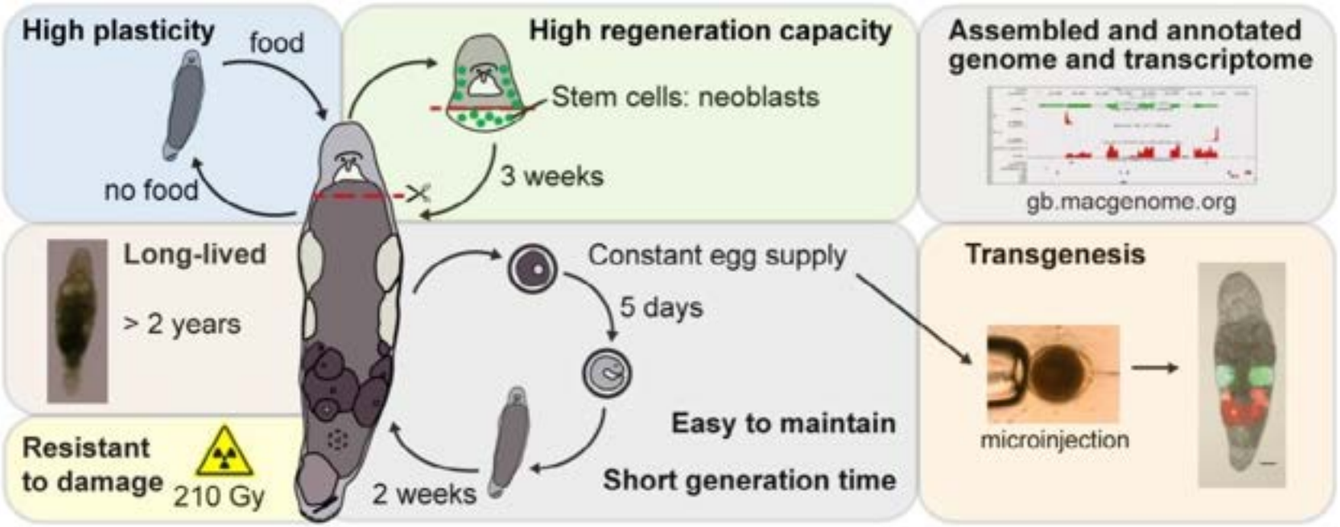


Figure.
The flatworm Macrostomum lignano is a versatile model organism to study stem cells, regeneration, ageing and resilience mechanisms. Adapted from Wudarski et al., EvoDevo 11:5 (2020).

The Future

Regeneration is an efficient organismal resilience strategy to injury but understanding its mechanisms is still incomplete. Using the power of transgenesis in *M. lignano*, combined with single-cell sequencing and comparative genomics, we plan to characterize regulatory programs that drive cell fate specification during regeneration. Furthermore, we plan to investigate how *M. lignano* survives high doses of gamma- and UVC radiation and test whether resilience-associated *Macrostomum* genes can confer similar resilience in other animals.

Stem cell regulation and mechanisms of regeneration

Eugene Berezikov

Selected Publication

Stijn Mouton, Alexandra Mougel, Kirill Ustyantsev, Colette Dissous, Oleg Melnyk, **Eugene Berezikov**, Jérôme Vicogne
Optimized protocols for RNA interference in *Macrostomum lignano*
G3 (Bethesda). 2024 May 7;14(5):jkae037.
doi: 10.1093/g3journal/jkae037.

Macrostomum lignano, a marine free-living flatworm, has emerged as a potent invertebrate model in developmental biology for studying stem cells, germline, and regeneration processes. In recent years, many tools have been developed to manipulate this worm and to facilitate genetic modification. RNA interference is currently the most accessible and direct technique to investigate gene functions. It is obtained by soaking worms in artificial seawater containing dsRNA targeting the gene of interest. Although easy to perform, the original protocol calls for daily exchange of dsRNA solutions, usually until phenotypes are observed, which is both time- and cost-consuming. In this work, we have evaluated alternative dsRNA delivery techniques, such as electroporation and osmotic shock, to facilitate the experiments with improved time and cost efficiency. During our investigation to optimize RNAi, we demonstrated that, in the absence of diatoms, regular single soaking in artificial seawater containing dsRNA directly produced in bacteria or synthesized in vitro is, in most cases, sufficient to induce a potent gene knockdown for several days with a single soaking step. Therefore, this new and highly simplified method allows a very significant reduction of dsRNA consumption and lab work. In addition, it enables performing experiments on a larger number of worms at minimal cost.

Group Members

Lisa Glazenburg Technician
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Kirill Ustyantsev Research Associate
Joscha Muck Postdoc
Mattia Stranges PhD student

Gene regulation in ageing and age-related diseases

Cor Calkhoven

Introduction

Our research aim is to identify and understand the role of regulatory networks that control the function of C/EBPα and C/EBPβ transcription factors in ageing and age-related diseases. We showed that mRNA-translational regulation of C/EBPβ expression through the mTORC1 nutrient and energy signaling pathway are linked to ageing and health- and lifespan determination. Others showed that deficiency of DNA-demethylation factors that regulate access of C/EBPβ to its genome binding sites result in premature ageing. In addition, the NAD+-SIRT1 pathway controls the function in mitochondrial biogenesis and respiration through regulation of C/EBPα protein-deacetylation. Apart from its physiologic metabolic functions, we study the oncogenic functions of C/EBPβ in promoting cancer metabolism, cell migration and immune evasion, particular in breast cancer. In another line of research, we study the pro-tumorigenic role of TSC-mTORC1 regulation in small cell lung cancer and its potential value as a therapeutic target.

Gene regulation in ageing and age-related diseases

Cor Calkhoven

Research Focus

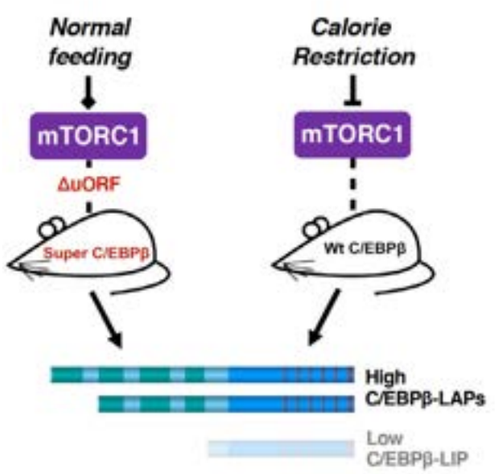
The CEBPA- and CEBPB-mRNAs are translated into full length, active transcription factors, C/EBPβ-LAP and C/EBPα-p42, as well as shorter inhibitory isoforms, C/EBPβ-LIP and C/EBPα-p30. A single upstream open reading frame (uORF) in these mRNAs functions as a cis-regulatory element necessary for translation into C/EBPβ-LIP and C/EBPα-p30, making them sensitivity to specific translational regulation pathways, particularly mTORC1 nutrient signaling. We have shown that disrupting mTORC1-mediated regulation of C/EBPβ-LIP by removing the uORF leads to significant delays in a wide range of age-related conditions in mice. These effects are comparable to those observed with calorie restriction or other mTOIRC1-inhibitory interventions (Figure). This $Cebpb^{\Delta uORF}$ mutation confers "C/EBPβ super-function", as only the transactivating LAP isoform is expressed, remaining unaffected by the inhibitory C/EBPβ-LIP. Similarly, we showed that C/EBPα-p30 expression is regulated in the same way, and removal of the uORF results in "C/EBPα super-function" in cell culture models. In addition to mTORC1, we identified other pathways that regulate C/EBPβ-LIP, such as eIF2α-kinases and the RNA demethylase FTO.

Another significant regulation of C/EBPα function occurs through lysine acetylation. The acetylation status of C/EBPα is modulated through deacetylation by SIRT1, in response to changes in NAD+ homeostasis. Hypoacetylated C/EBPα enhances the transcription of mitochondrial genes, leading to increased mitochondrial function and identifying C/EBPα as a key mediator of SIRT1-controlled adaption of energy homeostasis. Preliminary data of studies deciphering the molecular mechanisms behind the differential gene regulation by hypo- versus hyperacetylation C/EBPα suggest the involvement of cofactor switching.

In a separate line of research, we discovered that oncogenic MYC restrains mTORC1 signaling in Burkitt's lymphoma by safeguarding the expression of the tuberous sclerosis complex (TSC). Disruption of MYC-TSC1-mTORC1 regulation leads to increased mitochondrial respiration, accumulation of toxic reactive oxygen species, and cell death. Our current studies reveal that TSC expression is also elevated in small cell lung cancer, and we currently investigate its tumor promoting role and involved regulatory and pathological mechanisms.

Gene regulation in ageing and age-related diseases

Cor Calkhoven



Metababolic trait	C/EBPβ –ΔuORF	Calorie restricted
Body weight	↓	↓
Fat content	↓	↓
Steatosis	↓	↓
Adiponectin	↑	↑
Glucose	↓	↓
Insulin	↓	↓
Glucose tol.	↑	↑
Ins. sensitivity	↑	↑
GH/IGF-1	↓	↓

Ageing phenotypes	C/EBPβ –ΔuORF	Calorie restricted
Rotarod	↑	↑
Beam walking	↑	↑
Wire hang	↑	↑
naïve/memory T-cells	↑	↑
Better maintained during ageing (4 vs. 20 months)		
Cancer	↓	↓

Figure.
The table shows a compilation of phenotypes induced by the CebpbΔuORF mutation resulting in C/EBPβ super-function through loss of LIP expression. Similar metabolic phenotypes and delay in age-related conditions can be achieved by calorie restriction.

The Future

Triple-negative breast cancer (TNBC) cells express high levels of C/EBPβ-LIP, which is independent of mTORC1 signaling. This upregulation contributes to TNBC cell proliferation, migration, and immune evasion. Our research aims to identify the oncogenic pathways driving C/EBPβ-LIP overexpression and uncovering the mechanisms underlying TNBC development and immune escape. We are investigating the role of mTORC1- and SIRT1-mediated regulation of C/EBPα health and lifespan using genetic engineered mouse and killifish models. Furthermore, we have identified RNA methylation as a new regulatory mechanism for C/EBPs, along with other factors involved in metabolism and cancer, which will require further investigation. Finally, we have uncovered tumor-maintenance functions of TBC1D7 in small cell lung cancer (SCLC) as part of the tuberous sclerosis complex (TSC1/TSC2/TBC1D7). The involved mechanisms and therapeutic potential will be further investigated. As part of both the C/EBP and TSC projects, we aim to develop drug screening strategies to identify new therapies for metabolic disorders and cancer.

Gene regulation in ageing and age-related diseases

Cor Calkhoven

Selected Publication

Ackermann, T., Zuidhof, H.R., Müller, C., Kortman, G., Rutten, M.G.S., Broekhuis, M.J.C., Zaini, M.A., Hartleben, G. and **Calkhoven, C.F.** (2023)
C/EBPβ-LIP mediated activation of the malate-aspartate shuttle sensitizes cells to glycolysis inhibition.
Mol Metab.
doi: 10.1016/j.molmet.2023.101726

Objective Cancer cells use glycolysis for generation of metabolic intermediates and ATP needed for cell growth and proliferation. The transcription factor C/EBPβ-LIP stimulates glycolysis and mitochondrial respiration in cancer cells. We initially observed that high expression of C/EBPβ-LIP makes cells vulnerable to treatment with the glycolysis inhibitor 2-deoxyglucose. The aim of the study was to uncover the involved mechanisms of C/EBPβ-LIP induced sensitivity to glycolysis inhibition.

Methods We used genetically engineered cell lines to examine the effect of C/EBPβ-LIP and -LAP protein isoforms on glycolysis and NADH/NAD+ metabolism in mouse embryonic fibroblasts (MEFs), and triple negative breast cancer (TNBC) cells that endogenously express high levels of C/EBPβ-LIP. Analyses included assays of cell proliferation, cell survival and metabolic flux (OCR and ECAR by Seahorse XF96). Small molecule inhibitors were used to identify underlying metabolic pathways that mediate sensitivity to glycolysis inhibition induced by C/EBPβ-LIP.

Results The transcription factor C/EBPβ-LIP stimulates both glycolysis and the malate-aspartate shuttle (MAS) and increases the sensitivity to glycolysis inhibition (2-deoxyglucose) in fibroblasts and breast cancer cells. Inhibition of glycolysis with ongoing C/EBPβ-LIP-induced MAS activity results in NADH depletion and apoptosis that can be rescued by inhibiting either the MAS or other NAD+-regenerating processes.

Conclusion This study indicates that a low NADH/NAD+ ratio is an essential mediator of 2-deoxyglucose toxicity in cells with high cytoplasmic NAD+-regeneration capacity and that simultaneous inhibition of glycolysis and lowering of the NADH/NAD+ ratio may be considered to treat cancer.

Group Members

Christine Müller Senior scientist
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Jasmijn Woudenberg MSc student
Gertrud Kortman Technician

Molecular neurobiology of ageing

Ellen Nollen

Introduction

Maintenance of protein homeostasis is essential for cellular health but during aging cellular maintenance mechanisms become less effective. Due to this loss of protein homeostasis, aggregation-prone proteins accumulate, which are toxic to cells and can cause disease. The biological mechanisms that drive such age-related protein toxicity are still incompletely understood. Our aim is to uncover these mechanisms and identify targets for biomedical interventions that prevent or delay age-related protein toxicity in aging and age-related diseases.

Molecular neurobiology of ageing

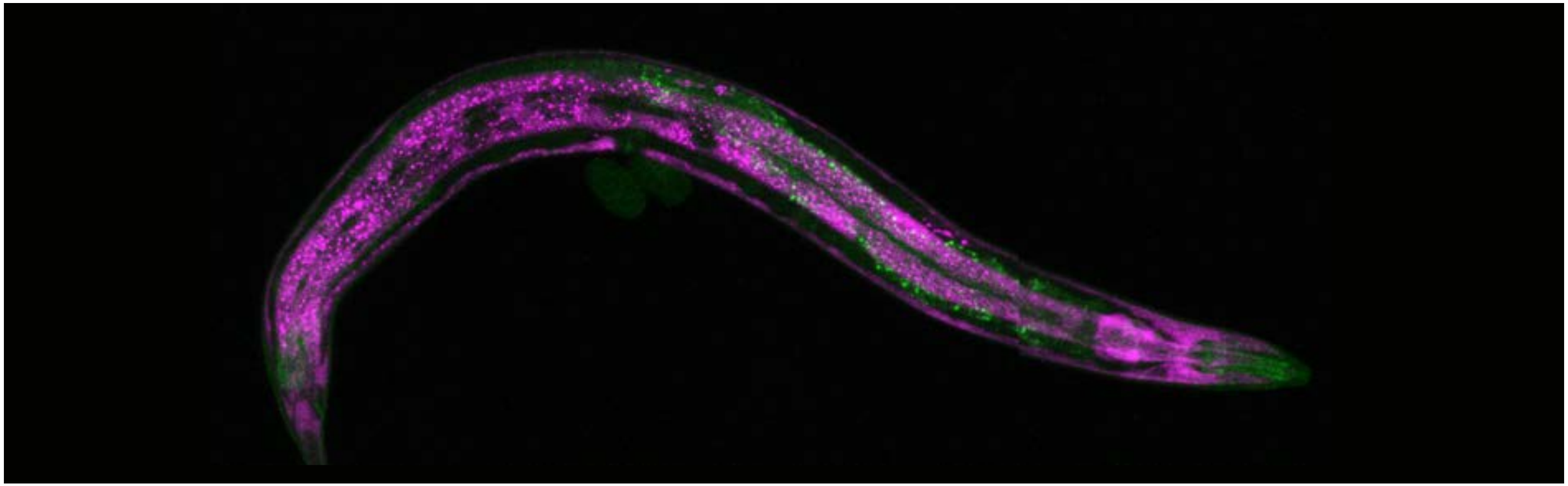
Ellen Nollen

Research Focus

Our research focusses on aggregation-prone proteins that are characteristic of proteinopathies like Parkinson, Alzheimer's and ALS, which include alpha-synuclein, amyloid-beta, and TDP-43, and the mechanisms that drive their toxicity. Using genetic and phenotypic screens in C. elegans models, we have identified several evolutionary conserved mechanisms that, when inhibited, suppress the toxicity of such disease proteins. These include cellular factors like MOAG-4/SERF that drives toxicity through direct, charge-driven, interactions with aggregation-prone proteins. In addition, we identified metabolic factors, such as the tryptophan di-dioxygenase TDO, for which we currently aim to understand how its inhibition protects against protein toxicity. We have recently developed a phenotypic screening pipeline and tools to monitor the consequences of aggregation-prone proteins for health and behavior. We are using this pipeline to uncover and understand the mechanisms involved in protein toxicity. Furthermore, we take advantage of our technology to explore how other systemic and environmental factors, such as neuronal circuits and microbiome-host interactions converge at such proteotoxic mechanisms.

Molecular neurobiology of ageing

Ellen Nollen



A C. elegans worm expressing TDO tagged with a fluorescent marker (visible in pink).

Image credit: ***Anna Ainslie***

The Future

We will continue our search for biological modifiers and their modes of action and, together with clinical and industrial partners, hope to find targets for interventions that protect or increase resilience to age-related protein toxicity.

Molecular neurobiology of ageing

Ellen Nollen

Selected Publication

Koopman M, Güngördü L, Janssen L, Seinstra RI, Richmond JE, Okerlund N, Wardenaar R, Islam P, Hogewerf W, Brown AEX, Jorgensen EM, **Nollen EAA**. **Rebalancing the motor circuit restores movement in a Caenorhabditis elegans model for TDP-43 toxicity**. Cell Rep. 2024 May 28;43(5):114204. doi: 10.1016/j.celrep.2024.114204. Epub 2024 May 14. PMID: 38748878.

Amyotrophic lateral sclerosis can be caused by abnormal accumulation of TAR DNA-binding protein 43 (TDP-43) in the cytoplasm of neurons. Here, we use a C. elegans model for TDP-43-induced toxicity to identify the biological mechanisms that lead to disease-related phenotypes. By applying deep behavioral phenotyping and subsequent dissection of the neuromuscular circuit, we show that TDP-43 worms have profound defects in GABA neurons. Moreover, acetylcholine neurons appear functionally silenced. Enhancing functional output of repressed acetylcholine neurons at the level of, among others, G-protein-coupled receptors restores neurotransmission, but inefficiently rescues locomotion. Rebalancing the excitatory-to-inhibitory ratio in the neuromuscular system by simultaneous stimulation of the affected GABA- and acetylcholine neurons, however, not only synergizes the effects of boosting individual neurotransmitter systems but instantaneously improves movement. Our results suggest that interventions accounting for the altered connectome may be more efficient in restoring motor function than those solely focusing on diseased neuron populations.

Group Members

Anna Ainslie Postdoc
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Eugenia Goya Postdoc
Lale Güngördü PhD student
Alejandor Herron PhD student
Renée Seinstra Technician

Lab of gut-liver axis in healthy ageing

Folkert Kuipers

Introduction

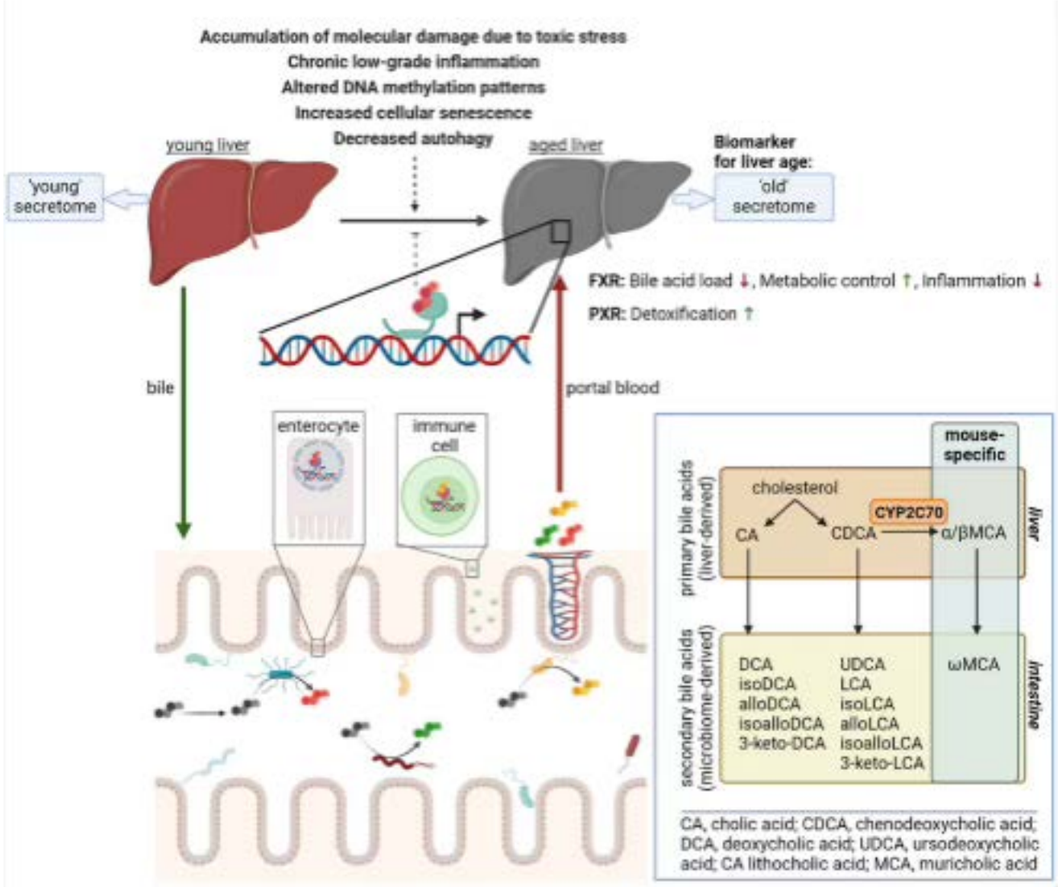
Heterogeneity in ageing processes that are manifest between individuals as well as between organs of an individual represents a very challenging aspect of ageing research that complicates design of healthspan promoting interventions. This challenge is further increased by the recognition of the gut microbiome as a highly dynamic metabolic and immunogenic 'organ' that strongly affects host health and resilience to environmental challenges. Disturbances in gut microbiome-host communication are now known to contribute to a variety of age-related pathological conditions, such as type 2 diabetes and cardiovascular diseases, i.e., conditions with an inflammatory component. It is now well-established that the composition of the microbiome gradually changes during human ageing leading to a decrease in ecological diversity, referred to as dysbiosis. The recent addition of dysbiosis to the list of hallmarks of ageing emphasizes its perceived importance for the biology of ageing. My research program "Gut-Liver Axis in Healthy Ageing" deals with molecular (dys)regulation of cholesterol, bile acid (BA) and lipid metabolism and transport in liver and intestine in inherited and age-related chronic metabolic diseases, including the various roles of the gut microbiome.

Lab of gut-liver axis in healthy ageing

Folkert Kuipers

Research Focus

We propose that the gut microbiome decisively impacts ageing processes in intestine and liver, at least in part through production of secondary BA species (see Figure) with specific physico-chemical characteristics and signaling functions and by modulating their flux within the enterohepatic circulation. The identification of multiple nuclear and membrane-bound receptors that are differentially activated by primary and secondary BAs, the identification of hitherto unknown secondary BAs and the discovery that primary and secondary BAs have different immune-modulating functions warrants further evaluation of their roles in ageing processes. Of great importance in this context are our findings that the composition of the circulating BA pool shows a very large intraindividual variations in healthy subjects, in elderly obese subjects, and in obese subjects with type 2 diabetes. The (patho)physiological relevance of this divergence is currently unknown. A common denominator of conditions associated with liver ageing phenotypes is the well-known age- and dysbiosis-associated impaired intestinal barrier function (leaky gut): increased intestinal permeability results in an enhanced flow of bacterial products (e.g., LPS) towards the liver to induce an inflammatory status that will accelerate liver ageing. Intriguingly, the BA-activated receptor FXR has been identified as a modulator of intestinal barrier function28, delineating the importance of strong inter-organ communication within the gut-liver axis.



Lab of gut-liver axis in healthy ageing

Folkert Kuipers

The Future

Exploration To identify nuclear receptor-mediated signaling pathways via which microbiome-derived secondary BAs modulate hallmarks of ageing in the liver and define the roles of BA-activated nuclear receptors in ageing phenotypes in intestine and liver of C57Bl6 mice with a human-like BA pool composition.

Modulation To assess the impact of interventions that prolong healthspan on microbial BA metabolism and on BA-activated nuclear receptor-mediated signaling pathways in intestine and liver the host.

Translation To assess the relevance of BA signaling pathways identified as putative ageing-modulating pathways in the human liver.

Lab of gut-liver axis in healthy ageing

Folkert Kuipers

Selected Publication

Hilde D de Vries, Tim R Eijgenraam, Vincent W Bloks, Niels L Mulder, Tim van Zutphen, Herman H W Silljé, **Folkert Kuipers**, Jan Freark de Boer
Elevated plasma bile acids coincide with cardiac stress and inflammation in young Cyp2c70-/- mice
Pediatr Res 2024
doi: 10.1038/s41390-024-03596-4.
Online ahead of print. PMID: 39358409

Background High plasma bile acids (BAs), for instance due to intrahepatic cholestasis of pregnancy or neonatal cholestasis, are associated with cardiac abnormalities. Here, we exploited the variability in plasma BA levels in Cyp2c70-/- mice with a human-like BA composition to investigate the acute effects of elevated circulating BAs on the heart.

Methods RNA sequencing was performed on hearts of 3-week-old Cyp2c70-/- mice lacking mouse-specific BA species that show features of neonatal cholestasis. Cardiac transcriptomes were compared between wild-type pups, Cyp2c70-/- pups with low or high plasma BAs, and Cyp2c70-/- pups from dams that were perinatally treated with ursodeoxycholic acid (UDCA). Results: We identified 1355 genes that were differentially expressed in hearts of Cyp2c70-/- mice with high versus low plasma BAs with enrichment of inflammatory processes. Strikingly, expression of 1053 (78%) of those genes was normalized in hearts of pups of UDCA-treated dams. Moreover, 645 cardiac genes strongly correlated to plasma BAs, of which 172 genes were associated with cardiovascular disease.

Lab of gut-liver axis in healthy ageing

Folkert Kuipers

Selected Publication

Hilde D de Vries, Tim R Eijgenraam, Vincent W Bloks, Niels L Mulder, Tim van Zutphen, Herman H W Silljé, **Folkert Kuipers**, Jan Freark de Boer
Elevated plasma bile acids coincide with cardiac stress and inflammation in young Cyp2c70-/- mice
Pediatr Res 2024
doi: 10.1038/s41390-024-03596-4.
Online ahead of print. PMID: 39358409

Conclusions Elevated plasma BAs alter gene expression profiles of hearts of mice with a human-like BA profile, revealing cardiac stress and inflammation. Our findings support the notion that high plasma BAs induce cardiac complications in early life.

Impact Cyp2c70-/- mice with a human-like bile acid composition show features of neonatal cholestasis but the extrahepatic consequences hereof have so far hardly been addressed. Elevated plasma bile acids in Cyp2c70-/- pups coincide with cardiac stress and inflammation. Perinatal treatment with UDCA prevents dysregulated cardiac gene expression patterns in Cyp2c70-/- pups.

Group Members

Brecht Attema post-doc
Ellen Weersing technician
In collaboration with Laboratory of Pediatrics

Telomeres and Genome Integrity

Michael Chang

Introduction

The overall goal of our lab is to characterize the mechanisms used by a cell to protect its genome from becoming mutated or inappropriately altered or rearranged. The genome is duplicated in a process called DNA replication. If DNA becomes damaged, either as a consequence of normal cellular processes or due to exposure to DNA damaging agents, DNA repair pathways are employed to fix the damage. Defective DNA replication or DNA repair results in genome instability, which is a hallmark of both cancer and ageing.

Telomeres and Genome Integrity

Michael Chang

Research Focus

Research in our lab is currently focussed on understanding how cells deal with DNA sequences—in particular, short tandem DNA repeat sequences—that are particularly challenging to replicate or repair. Short tandem DNA repeat sequences account for approximately 7% of the human genome. These sequences are often difficult to replicate, are prone to expansion and contraction, and can cause chromosomal rearrangements. Expansion of 15 different short tandem repeat sequences is linked to approximately 70 diseases, including Huntington's disease, Friedreich's ataxia, and fragile X syndrome, while chromosomal rearrangements are a source of genetic diseases and cancer. Misregulation of telomeric repeats, the best-studied example of a short tandem repeat sequence, is a hallmark of both cancer and ageing.

We examine the how such sequences are replicated and repaired in the budding yeast Saccharomyces cerevisiae, which is an ideal model organism given the highly conserved nature of DNA replication and repair processes and the experimental advantages of the yeast system. We aim to identify relevant genes, and to determine their function and relationship with one another.

Telomeres and Genome Integrity

Michael Chang

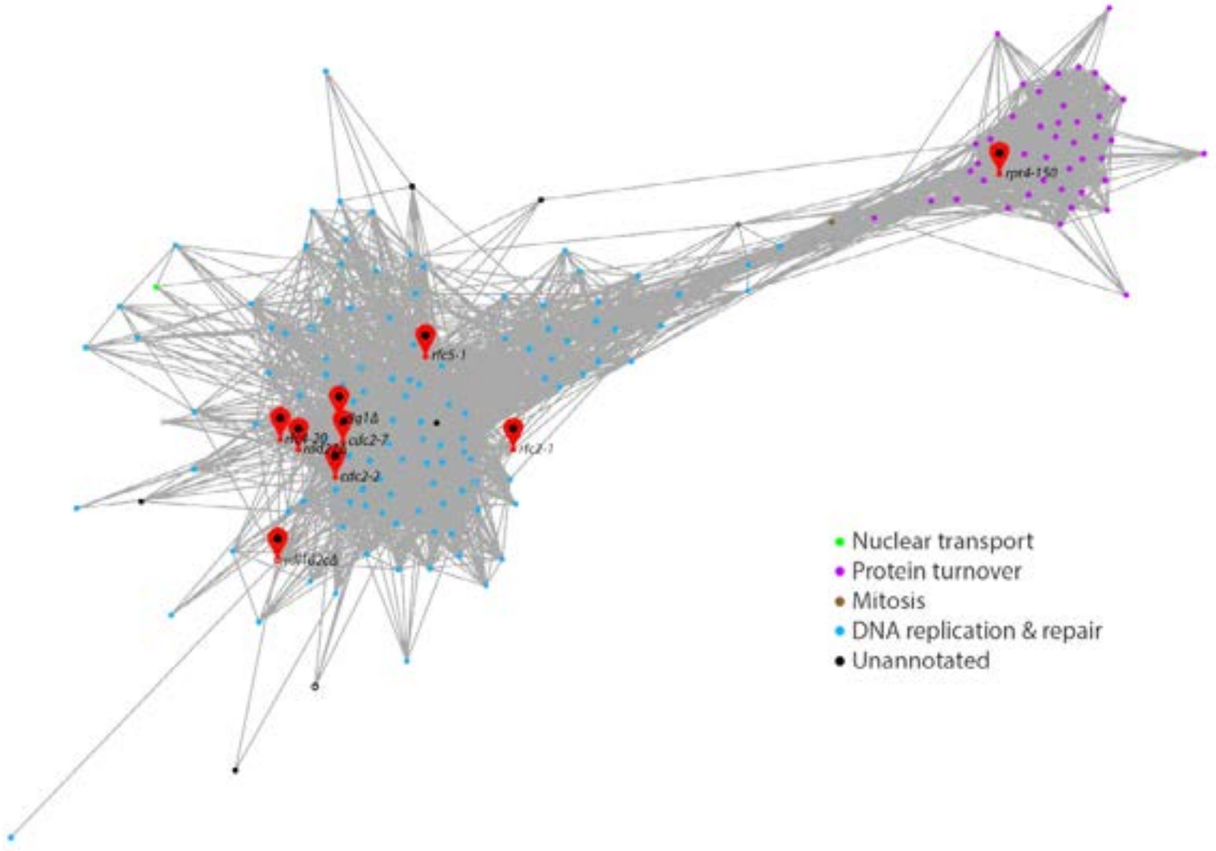


Figure.
Genetic interaction profile similarity subnetwork for genes that suppress gross chromosomal rearrangement induced by interstitial telomeric sequences. The network was generated using TheCellMap.org (Usaj et al., 2017; doi: 10.1534/g3.117.040220). Nodes (representing deletions of nonessential genes or temperature-sensitive alleles of essential genes) sharing similar genetic interaction profiles (PCC > 0.2) are connected by an edge in the network. Genes sharing similar genetic interaction profiles map closer to each other. The subnetwork was annotated using Spatial Analysis of Functional Enrichment (Baryshnikova, 2016; doi: 10.1016/j.cels.2016.04.014).

The Future

Our lab will continue to study how cells protect their genome from mutagenic alterations. In particular, we are focussed on understanding how repetitive DNA sequences, which pose unique obstacles for the DNA replication machinery, are dealt with by genome maintenance mechanisms.

Telomeres and Genome Integrity

Michael Chang

Selected Publication

Rosas Bringas, F.R.†, Yin, Z.†, Yao, Y., Boudeman, J., Ollivaud, S., and **Chang, M.** (2024) **Interstitial telomeric sequences promote gross chromosomal rearrangement via multiple mechanisms.** Proc. Natl. Acad. Sci. USA, 121(49): e2407314121. †Co-first author doi: 10.1073/pnas.2407314121

Telomeric DNA sequences are difficult to replicate. Replication forks frequently pause or stall at telomeres, which can lead to telomere truncation and dysfunction. In addition to being at chromosome ends, telomere repeats are also present at internal locations within chromosomes, known as interstitial telomeric sequences (ITSs). These sequences are unstable and prone to triggering gross chromosomal rearrangements (GCRs). In this study, we quantitatively examined the effect of ITSs on GCR rate in Saccharomyces cerevisiae using a genetic assay. We find that GCR rate increases exponentially with ITS length. This increase can be attributed to the telomere repeat binding protein Rap1 impeding DNA replication and a bias of repairing DNA breaks at or distal to the ITS via de novo telomere addition. Additionally, we performed a genome-wide screen for genes that modulate the rate of ITS-induced GCRs. We find that mutation of core components of the DNA replication machinery leads to an increase in GCRs, but many mutants known to increase GCR rate in the absence of an ITS do not significantly affect GCR rate when an ITS is present. We also identified genes that promote the formation of ITS-induced GCRs, including genes with roles in telomere maintenance, nucleotide excision repair, and transcription. Our work thus uncovers multiple mechanisms by which an ITS promotes GCR.

Group Members

Fleur Brakels
Silje Hoornveld
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Daniele Novarina
Mirjam Piekema
Sandra Ollivaud PhD Student
Maïmouna Tal
Yue Yao PhD Student
Ziqing Yin PhD Student

Cellular Senescence and Age-Related Pathologies

Marco Demaria

Introduction

Our research focuses on the mechanisms that regulate the induction and progression of cellular senescence, as well as the diverse physiological and pathological functions of senescent cells. Cellular senescence is a dynamic process characterized by stable growth arrest, which serves as a well-established tumor suppressive mechanism. However, this growth arrest can also impair the maintenance of essential cell populations with age, potentially contributing to tissue dysfunction and degenerative processes.

A defining feature of senescent cells is their secretion of a complex mixture of cytokines, growth factors, matrix metalloproteases, lipids, and nucleotides—collectively known as the senescence-associated secretory phenotype (SASP). The SASP plays a crucial role in tissue remodeling and repair during both embryonic development and adulthood and facilitates the efficient clearance of senescent cells by the immune system. However, accumulating evidence indicates that senescent cells persist in the tissues of aging organisms, where the SASP becomes a driver of chronic low-grade inflammation, aberrant tissue remodeling, and the progression of age-related diseases.

The recognition of the detrimental effects of senescent cells in aging and disease has spurred significant interest in therapeutic strategies to target them. In particular, the development of senolytic drugs—agents capable of selectively eliminating senescent cells—represents a promising avenue for mitigating the harmful effects of senescence while preserving its beneficial roles in homeostasis and repair.

Cellular Senescence and Age-Related Pathologies

Marco Demaria

Research Focus

Our laboratory has pioneered the concept of senescence heterogeneity and these findings, together with data from other laboratories, have demonstrated that senescence is not a uniform process but is regulated by a complex interplay of intrinsic and extrinsic factors. Importantly, we have defined that distinct subsets of senescent cells—each characterized by unique combinations of senescence-associated phenotypes—can co-exist in vivo. However, the specific molecular characteristics that define these different populations remain largely unknown, presenting an important challenge in the field.

To address this, we recently led an international consortium to establish guidelines for identifying different subsets of senescent cells in tissues (Ogrodnik et al., Cell 2024). Our goal is to delineate the beneficial and detrimental aspects of senescence by applying multi-omics approaches to models of injury, aging, and disease. To facilitate these investigations, we utilize senescence-reporter mice, including a novel inducible, tissue- and cell type-specific senescence reporter and ablation model. This advanced tool allows us to dissect the roles of senescent cells in different physiological and pathological contexts with greater precision.

Given that modulating senescence represents a promising strategy to promote health and delay age-related dysfunction, we are actively characterizing how small molecules, environmental conditions, and lifestyle interventions influence the accumulation of detrimental senescent cells with age. Beyond merely eliminating harmful senescent cells, we are also exploring ways to enhance beneficial senescence to support tissue regeneration and repair.

In a recent breakthrough, we identified a molecular switch that governs cell fate decisions between necrosis and senescence. By genetically or pharmacologically directing this switch toward senescence, we demonstrated reduced fibrosis and improved recovery from ischemic kidney injury (*Figure. Nehme et al., Nature Aging 2024*). This discovery underscores the potential of controlled senescence induction as a therapeutic approach to mitigate tissue damage and enhance repair mechanisms.

Cellular Senescence and Age-Related Pathologies

Marco Demaria

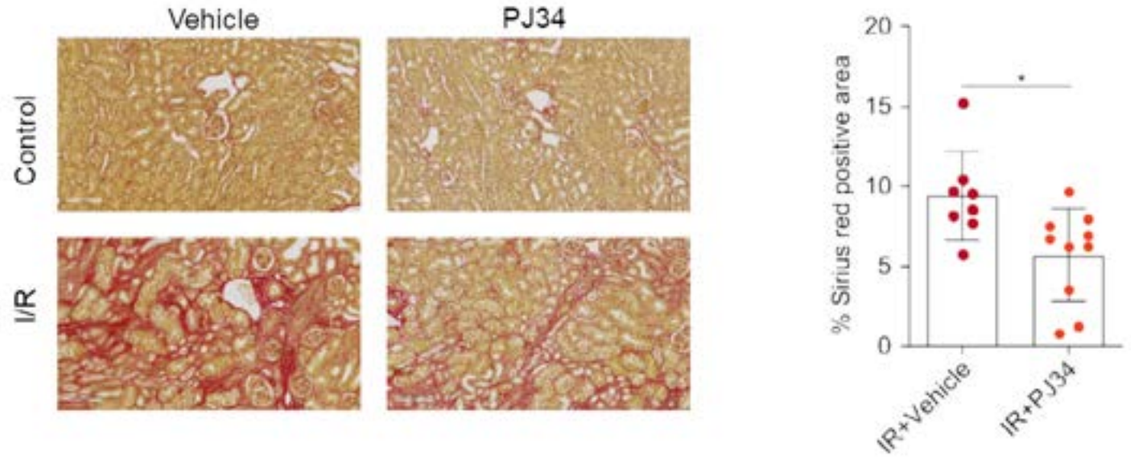

Figure.
Mice underwent unilateral kidney ischemia reperfusion (IR) injury with the administration of the PARP inhibitor PJ34 (10 mg kg–1) or vehicle. Kidney tissues were collected 35 days after induction of IR to analyze the long-term consequences of PARP inhibition. Sirius Red staining shows reduced fibrotic area (in red) of mice treated with PJ34.

The Future

Looking ahead, our research aims to expand the understanding of senescence heterogeneity by systematically analyzing and phenotyping distinct senescence subsets associated with specific physiological and pathological conditions. By dissecting the molecular signatures and functional diversity of these subsets, we seek to uncover how different forms of senescence contribute to tissue homeostasis, repair, aging, and disease progression.

A key emerging area of interest is the role of sexual dimorphism in senescence accumulation and function. Growing evidence suggests that sex-specific differences influence senescence dynamics, immune surveillance, and tissue resilience, yet the underlying mechanisms remain largely unexplored. Investigating these differences could provide critical insights into sex-specific aging trajectories and disease susceptibilities, ultimately leading to more personalized therapeutic strategies.

Our overarching goal is to advance the fundamental understanding of senescence while translating these insights into the development of innovative anti-aging and disease-modifying interventions.

Cellular Senescence and Age-Related Pathologies

Marco Demaria

Selected Publication

Converting cell death into senescence by PARP1 inhibition improves recovery from acute oxidative injury

doi: 10.1038/s43587-024-00627-x

Excessive amounts of reactive oxygen species (ROS) lead to macromolecular damage and high levels of cell death with consequent pathological sequelae.

We hypothesized that switching cell death to a tissue regenerative state could potentially improve the short-term and long-term detrimental effects of ROS-associated acute tissue injury, although the mechanisms regulating oxidative stress-induced cell fate decisions and their manipulation for improving repair are poorly understood. Here, we show that cells exposed to high oxidative stress enter a poly (ADP-ribose) polymerase 1 (PARP1)-mediated regulated cell death, and that blocking PARP1 activation promotes conversion of cell death into senescence (CODIS). We demonstrate that this conversion depends on reducing mitochondrial Ca2+ overload as a consequence of retaining the hexokinase II on mitochondria. In a mouse model of kidney ischemia–reperfusion damage, PARP inhibition reduces necrosis and increases transient senescence at the injury site, alongside improved recovery from damage. Together, these data provide evidence that converting cell death into transient senescence can therapeutically benefit tissue regeneration.

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Genomic Instability in Development and Disease

Floris Foijer

Introduction

Chromosomal instability (CIN) is a hallmark feature of cancer. CIN leads to cells with an abnormal DNA content, a state known as aneuploidy affecting >80% of all cancers. Paradoxically, in untransformed cells, CIN and aneuploidy decrease cellular fitness and lead to activation of stress pathways. This suggests that cancer cells have found ways to cope with the downsides of CIN. A better understanding of these coping strategies can lead to new therapies that target these mechanisms, and thus selectively kill the aneuploid cancer cells with fewer side effects on healthy cells. We study the how cells deal with chromosomal instability and aneuploidy, in vitro as well as in vivo. For this we 1) develop and exploit models and technology to faithfully measure chromosomal instability and aneuploidy in cultured cells as well as in living mice, 2) we develop mouse and advanced cell models to study CIN, which we 3) use to better understand the mechanisms that trigger the responses to CIN and 4) we exploit these mechanistic findings to design therapies that selectively kill cells with a CIN phenotype.

Genomic Instability in Development and Disease

Floris Foijer

Research Focus

Ongoing CIN leads to cells with variable karyotypes and thus to intratumour karyotype heterogeneity. CIN is therefore a strong driver of cancer cell evolution and associated with poor prognosis. Together with the research sequencing facility, we heavily invested in single cell DNA sequencing as a tool to quantify karyotype heterogeneity. We for instance used this tool to study how chromosomal instability drives the evolution of human cancers, for instance pediatric neuroblastoma or lymphoma (refs 1, 2). Furthermore, to better understand how chromosome missegregation affects the fitness of individual cells, we combine scWGS and scRNA-seq to better understand how individual karyotypes influence cellular fitness. For this, we take advantage of our earlier-published mouse models of CIN-induced T-ALL, from which we analyze primary tumor samples as well as T-ALL-derived cell lines, which is revealing that tumors with an ongoing CIN phenotype and semi-clonal karyotypes contain multiple smaller clones with unique karyotypes. We are currently investigating the biology of these smaller clones to better understand how chromosome missegregation drives cancer cell evolution, but also how CIN leads to cell populations that are less fit that ultimately will be selected against.

We recently found that CIN will trigger an inflammatory response in premalignant as well as cancer cells. Our work is indicating that this inflammatory response activates the immune system and thus leads to immune clearance of premalignant aneuploid cells. We find that cancer cells circumvent this inflammatory response by alleviating one of the main inflammatory routes in the cell: STAT1 signaling. This inflammatory response, triggered by CIN, critically relies on IL6 activity upstream of Stat1 and Stat3. In 2022, we showed that blocking IL6 signaling, e.g. by means of the clinically approved IL6R inhibitor tocilizumab is toxic to CIN tumor cells in vitro and in vivo, but well-tolerated by chromosomal stable cancers, revealing an unexpected Achilles heel of aneuploid cancers, which we are currently validating in models for T-ALL (funded by a Lymph&Co grant) and breast cancer (funded by a Vici grant). Furthermore, we are establishing mouse models in which we can knockout genes of choice using CRISPR in a tissue specific manner, also with a focus on breast cancer.

Genomic Instability in Development and Disease

Floris Foijer

To better understand how cells acquire resistance to CIN phenotypes, together with the Functional Genomics Center, we performed a CRISPR genome wide screen and found that inactivation of CDC20, an activator molecule of the Anaphase Promoting Complex (APC/c), decreases sensitivity to CIN-inducing drugs. Jointly with the Uri Ben-David lab (University Tel Aviv, Israel), we found that CDC20 is a modulator of the sensitivity to CIN with high levels of CDC20 being associated with CIN phenotypes in human cancer samples and low CDC20 levels leading to resistance to drugs that induce CIN. Together, this work identifies CDC20 as a potential biomarker of the response to CIN-inducing drugs in cancer therapy and as a potential target to lower CIN rates.

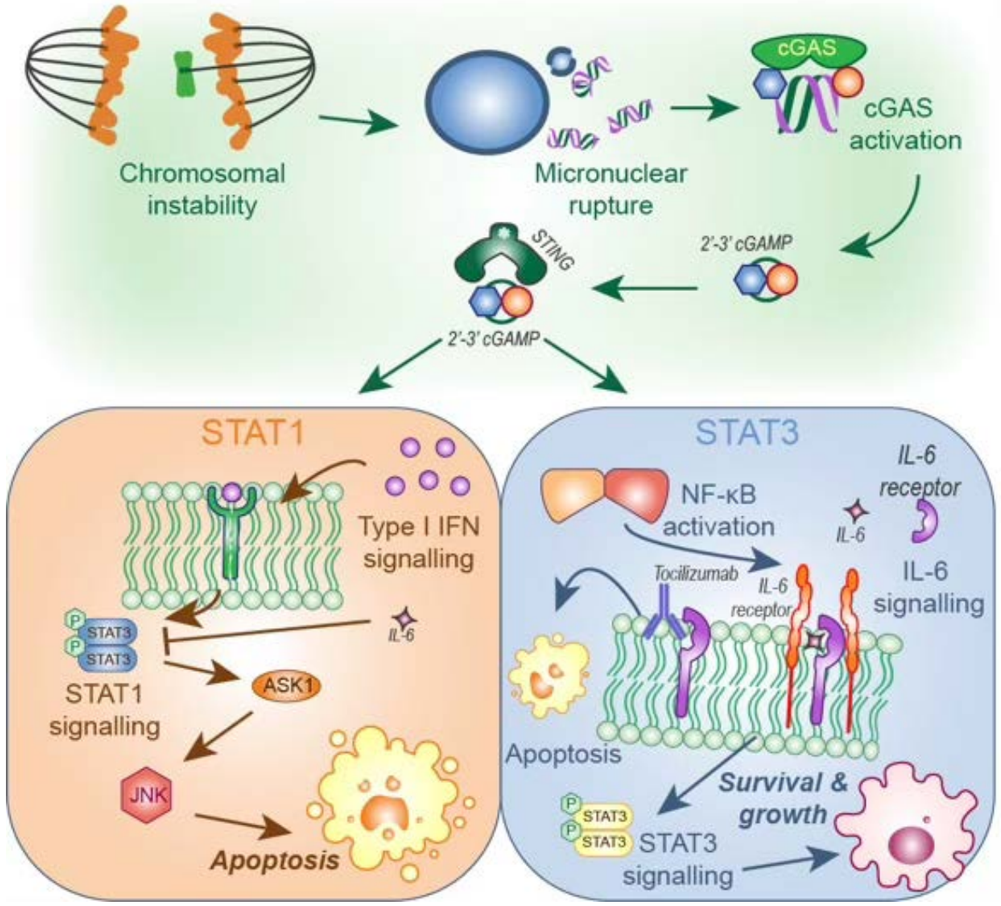

Figure.
CIN leads to a STAT1 pro-death and STAT3 pro-survival inflammatory response that can be selectively targeted to kill cells with CIN.

Genomic Instability in Development and Disease

Floris Foijer

The Future

Now that we identified that lack of immunosurveillance is an essential feature of tumors displaying a CIN phenotype, we next want to understand which immune cells clear aneuploid cells and which interactions between immune cells and cancer cells trigger clearance. Further, we want to map the molecular mechanisms that cancers exploit to inactivate immune signaling and translate this knowledge into therapeutic interventions that selectively target aneuploid cells. For this, we are developing state-of-the art cellular reporters to read out inflammation and techniques such as CUT&Tag to map the transitional response to CIN. In addition to mapping how immune cells clear aneuploid cells, we are further investigating the molecular mechanisms that trigger the initial inflammation response, including CRISPR genome-wide screens.

Furthermore, we want to better understand how karyotype dynamics drive tumor evolution. For this, we will investigate how chromosome copy number changes change cellular fitness in cell models, but also in vivo, including intravital imaging models to visualize aneuploidy in vivo in zebrafish and, ultimately, in mice. For this, we will develop fitness reporters as well as new zebrafish and mouse models in which we can determine cellular fitness in cultured cells including genome-wide screens as well as in vivo. Finally, in close collaboration with the newly established company iPsomics, we plan to investigate the potential of single cell genomics-inferred karyotype heterogeneity as a biomarker for the outcome of human cancers and a tool to stratify cancer treatment.

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Genomic Instability in Development and Disease

Floris Foijer

Selected Publication

Zheng S*, Raz L*, Zhou L*, Cohen-Sharir Y, Tian R, Ippolito MR, Gianotti S, Saad R, Wardenaar R, Broekhuis M, Suarez Peredo Rodriguez M, Wobben S, van den Brink A, Bakker P, Santaguida S, **Foijer F#**, Ben-David U#.
High CDC20 levels increase sensitivity of cancer cells to MPS1 inhibitors. EMBO Rep. 2025 Jan 21.
doi: 10.1038/s44319-024-00363-8.
Accepted Dec 2024

Spindle assembly checkpoint (SAC) inhibitors are a recently developed class of drugs, which perturb chromosome segregation during cell division, induce chromosomal instability (CIN), and eventually lead to cell death. The molecular features that determine cellular sensitivity to these drugs are not fully understood. We recently reported that aneuploid cancer cells are preferentially sensitive to SAC inhibition. Here we report that sensitivity to SAC inhibition by MPS1 inhibitors is largely driven by the expression of CDC20, a main mitotic activator of the anaphase-promoting complex (APC/C), and that the effect of CDC20 is larger than that of the APC/C itself. Mechanistically, we discovered that CDC20 depletion prolongs metaphase duration, diminishes mitotic errors, and reduces sensitivity to SAC inhibition. We found that aneuploid cells express higher basal levels of CDC20, which shortens the duration of metaphase and leads to multiple mitotic errors, resulting in increased long-term sensitivity to the additional CIN induced by SAC inhibition. Our findings propose high CDC20 expression as a molecular feature associated with the sensitivity to SAC inhibition therapy and as a potential aneuploidy-induced cellular vulnerability.

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Genome Structure and Ageing

Victor Guryev

Introduction

Even though the completion of the human genome project was announced over 20 years ago, our knowledge of genome variants and their effects on the onset of ageing-related diseases is still far from being complete. Under-investigated large and complex alterations in our genomes affect many more DNA bases than small, single-nucleotide changes. Some of these structural genome changes can be predicted using a routine analysis procedure of DNA data, others, like large inversions or non-reference insertions, deserve further investigation.

Our research aims to identify a wide spectrum of DNA alterations, fine-map them to corresponding genomic locations, and characterize their effects on molecular function. Our group combines analysis of genome, transcriptome, and proteome profiling (functional genomics and proteogenomics approaches) to distinguish deleterious genomic variants from benign ones. These results should contribute to a better understanding of the content, function of variable segments in our genomes, their role in ageing-related diseases.

Genome Structure and Ageing

Victor Guryev

Research Focus

Our research is focused on several approaches for investigating ageing-related molecular changes:

A. Investigation of genome alterations potentially associated with ageing-related diseases (*Figure 1 A)*. We are studying the distribution and role of large variants in our genomes. My team applies expertise developed in the Dutch genome project to characterize SVs in patients suffering from early-onset severe COPD, cancer, and other diseases.

B. Transcriptome regulation in ageing and onset of diseases (*Figure 1 B*). Previous studies already identified several trends (e.g. more retained introns) in transcriptome processing that happen as we get older. Our group analyses transcriptomes of several patient cohorts to identify sources of these changes and their potential roles in disease etiology.

C. Combining differential expression and differential variability analysis (*Figure 1 C*). Since many human diseases are very heterogeneous in their molecular and clinical manifestations, molecular subtyping and analysis of differential variability provide orthogonal approaches to classical disease association methods. We successfully employed methods for quantifying biological variability to get insight into cellular processes affected by ageing, lung diseases, sepsis, and COVID-19.

D. Multi-level data integration for personalized diagnostics and treatment (*Figure 1 D*). Combining DNA variation data with other omics layers, such as gene expression, proteomics, metabolomics, and phenotypic data, is key for the discovery of function for DNA polymorphisms. Previously, we used a rat model of hypertension to demonstrate that such analysis of DNA, RNA, and proteins, where information 'flows' across omics-layers, is an efficient way to study disease (PMID:24290761). This observation supports the validity of our approach and suggests that it can be useful for studying relations between structural genome variants and molecular phenotypes that manifest themselves at RNA and protein levels and potentially play roles in human diseases.

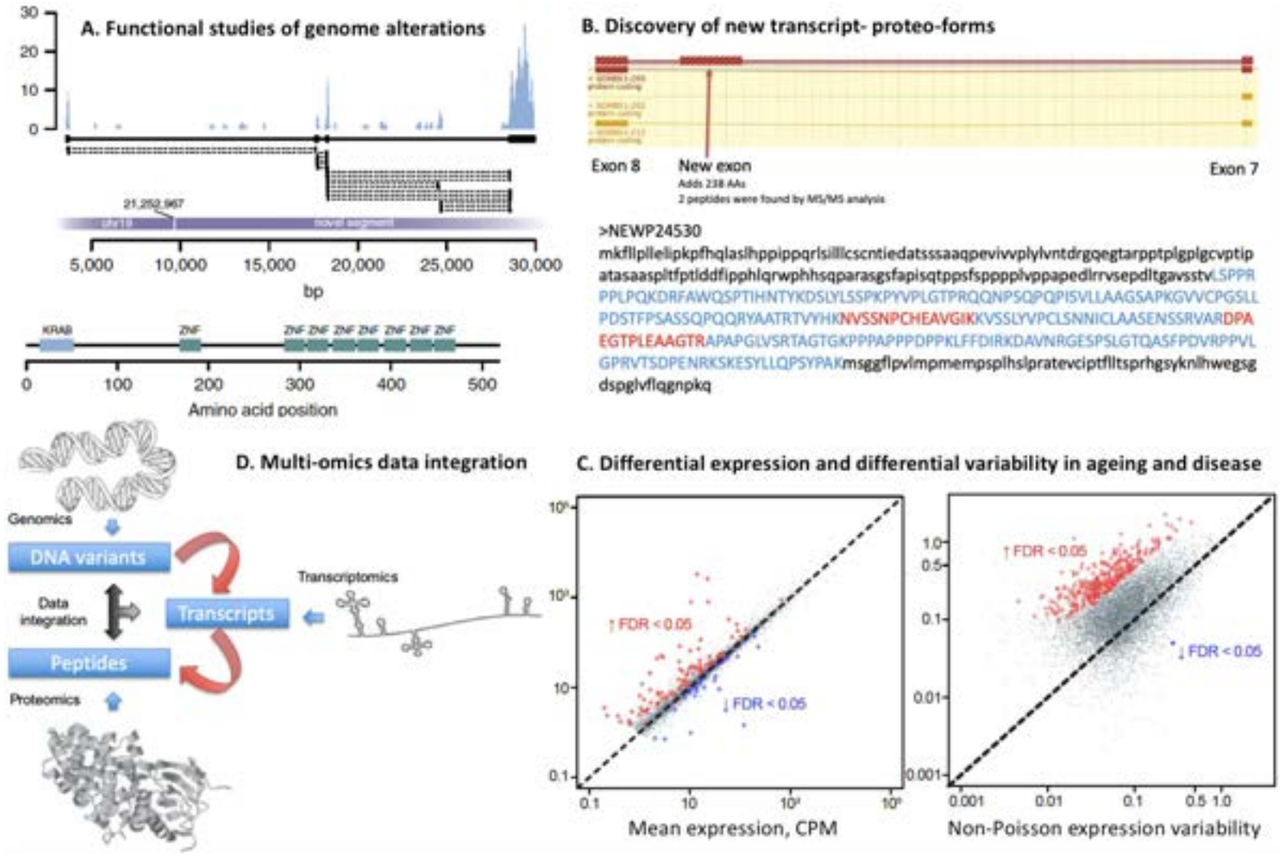

Figure 1.
Major research directions. (A). Investigation and functional characterization of large genome alterations and their role in the onset of age-related diseases. An example of a long non-reference insert on chr19, that encodes for a new zinc finger gene. Transcript coverage by RNA-seq reads (top), reads supporting splicing events (middle), and domain structure of resulting protein product (bottom) are displayed. (B) Transcriptome analysis identifies new disease-associated protein-coding exons. An example of an exon in the SORBS1 gene that is differentially present in transcripts of COPD patients. The exon adds 238 amino acids to the protein product and was confirmed by 2 corresponding peptides (in red) with LC-MS/MS data. (C) Differential expression and differential variability analysis show age-specific changes in gene expression. Left panel: more genes show upregulation of expression level in old individuals (y-axis) compared to young (x-axis). Right panel: many more genes show an increase in inter-individual variability in old individuals (y-axis) than in young individuals (x-axis). (D) Our multi-omics data integration approach. A common analysis strategy is to perform separate analyses for each omics level using public reference (black arrows). In our studies, we perform sequential integration where each omics layer informs the analysis of the next levels by providing data on DNA variants (genomics), splice variants, and new transcript units (transcriptome) for better interpretation of ageing- and disease-related molecular changes.

Genome Structure and Ageing

Victor Guryev

The Future

In the future, we aim to improve the prediction of functional consequences for large genome alterations in relation to human diseases. We plan to identify new transcriptional units and novel isoforms for known genes and link them to genome variation and dysregulated splicing factors (age- and disease-specific). Our short-term goal is to employ pathway and biochemical complex-centered analysis of gene expression variability. This will allow us to identify disruptions in particular gene ensembles on human diseases and better understand the underlying mechanism. Finally, we will continue to develop our computational framework for personalized multi-omics data integration and will utilize it for the analysis of omics data from other ageing-related diseases.

Genome Structure and Ageing

Victor Guryev

Selected Publication

Khalenkow et al, 2024.
Alternative Splicing Is a Major Factor Shaping Transcriptome Diversity in Mild and Severe Chronic Obstructive Pulmonary Disease.
Am J Respir Cell Mol Biol. 2024. 70:414-423.
doi: 10.1165/rcmb.2023-0296OC.

The study was initiated by a postdoc in our group (D. Khalenkow) and is a product of collaboration with clinical departments of UMCG and international teams. Chronic Obstructive Pulmonary Disease (COPD) is a common disease of the elderly associated with accelerated ageing of the lungs. Previous studies showed that lungs of COPD patients exhibit large changes in gene expression programs and multiple genes were seen to be up- or down-regulated in previous studies. However, another aspect of transcriptome changes, the switching of transcript isoforms, was under-investigated. We found that the composition of splicing events depends on disease severity and the splicing alterations have a higher impact in patients with severe disease. Interestingly, such changes lead to an increase in protein-coding (compared to non-coding) isoforms. Further, transcripts from severe COPD patients show a decrease in intron retention events, an opposite trend to that observed in ageing. This suggests that splicing alterations are not solely the result of COPD-related accelerated aging. We also identified a set of splicing factors that could drive the isoform switching. Our findings suggest that alternative splicing is a major factor defining COPD transcriptome and future studies of patients' transcriptomes should not be limited to expression levels, but also involve analysis of isoform composition.

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Cellular Biochemistry

Liesbeth Veenhoff

Introduction

The main research line in the group is to understand the role of the nuclear pore complex (NPC) in ageing. The NPCs are the sole gateways to the interior of the nucleus and their function is essential to all eukaryotic life. The NPC's function is intimately connected to the primary hallmarks of ageing of protein homeostasis and genome stability. We made contributions to the understanding of the structure and function of NPCs and in uncovering the vulnerabilities of NPCs in ageing cells. The surveillance of the intrinsically disordered proteins of the NPC is a main interest in the lab, as it appears that mechanisms that guard their structural state, also guard other intrinsically disordered proteins related to aggregation pathologies. This provides a new entry into the problem of protein aggregation pathologies and ageing. Complementing these studies aiming to uncover how the quality control of NPCs and intrinsically disordered proteins can be better safeguarded in ageing, we aim to contribute to a better understanding of the cellular ageing process in general.

Cellular Biochemistry

Liesbeth Veenhoff

Research Focus

Surveillance of intrinsically disordered proteins in ageing

The NPC's function is intimately connected to the primary hallmarks of ageing of proteins homeostasis and genome stability, and several processes underlying these hallmarks are orchestrated at NPCs. The NPC's function is compromised in ageing and age-related aggregation pathologies, and we aim to uncover the mechanisms responsible for NPC quality control.

The NPC is a prime example of a molecular machine whose function relies on intrinsically disordered proteins, proteins that lack a persistent secondary or tertiary structure. The intrinsically disordered proteins of NPCs are named FG-nucleoporins (FG-Nups) and they form a selective barrier. Away from the NPC, FG-Nups readily form condensates and aggregates, and we address how this behavior is surveilled in cells. In, Otto et al. we address how the reduced expression of the intrinsically disordered FG-nucleoporin Nsp1 in aged cells relates to age-related nuclear pore complex assembly problems. We find that Nsp1 acts as a phase-state modulator, promoting a liquid-like state of FG-nucleoporin condensates and impacting general protein homeostasis (*Figure*).

Cellular Biochemistry

Liesbeth Veenhoff

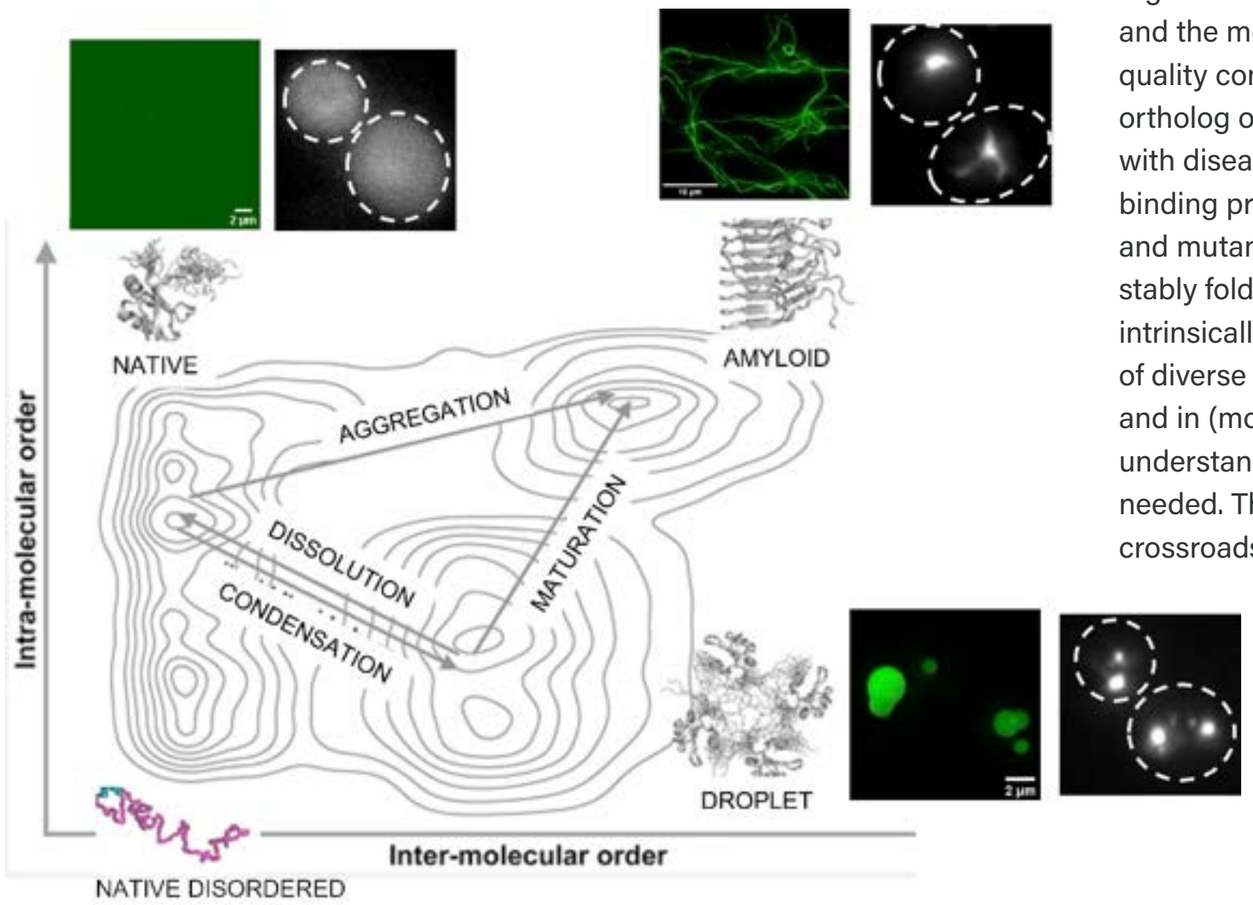

Figure.
Different phase states of intrinsically disordered proteins, adapted from Fuxreiter and Vendruscolo, 2021. Fluorescent images depict the phase states of purified FG-Nups in vitro and when expressed in yeast cells (Gallardo, Bergsma, unpublished).

Our data contribute to a larger emerging theme of a tightly regulated interplay between FG-Nups, nuclear transport factors, and the molecular chaperones from the classical protein quality control system. Interestingly, Nup62, the mammalian ortholog of Nsp1, has been found to participate in assemblies with disease-related IDPs, such as Transactive response DNA-binding protein of 43 kDa (TDP43), fused in sarcoma (FUS) and mutant Huntingtin. In general, protein quality control of stably folded proteins is much better understood than that of intrinsically disordered proteins. Aberrant phase state transitions of diverse intrinsically disordered proteins occurs in aged cells and in (models of) neurodegenerative diseases, and a better understanding of what regulates these transitions is much needed. This study identifies Nsp1 as a new player at these crossroads of NPC biology and protein quality control.

Cellular Biochemistry

Liesbeth Veenhoff

The Future

We will continue to design our research from the viewpoint that studying "biology in time" is an unbiased way to reveal fundamental knowledge; knowledge that is needed to combat age-related diseases. Specifically, we aim to identify the proteins that detect damaged NPCs, to know the destiny of damaged NPCs, and to uncover the mechanisms that prevent damage to NPCs. Understanding how condensation of intrinsically disordered proteins is surveilled will also remain a main interest in the lab.Together, the planned research aims to uncover how the quality control of NPCs and intrinsically disordered proteins can be better safeguarded in ageing.

Selected Publication

Otto TA, Bergsma T, Dekker M, Mouton SN, Gallardo P, Wolters JC, Steen A, Onck PR, **Veenhoff LM.**
Nucleoporin Nsp1 surveils the phase state of FG-Nups.
Cell Rep. 2024 Oct 22;43(10):114793

Transport through the nuclear pore complex (NPC) relies on intrinsically disordered FG-nucleoporins (FG-Nups) forming a selective barrier. Away from the NPC, FG-Nups readily form condensates and aggregates, and we address how this behavior is surveilled in cells. FG-Nups, including Nsp1, together with the nuclear transport receptor Kap95, form a native daughter cell-specific cytosolic condensate in yeast. In aged cells, this condensate disappears as cytosolic Nsp1 levels decline. Biochemical assays and modeling show that Nsp1 is a modulator of FG-Nup condensates, promoting a liquid-like state. Nsp1's presence in the cytosol and condensates is critical, as a reduction of cytosolic levels in young cells induces NPC defects and a general decline in protein quality control that quantitatively mimics aging phenotypes. These phenotypes can be rescued by a cytosolic form of Nsp1. We conclude that Nsp1 is a phase state regulator that surveils FG-Nups and impacts general protein homeostasis.

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Macromolecules and Interactomes

John LaCava

Introduction

Our group has a specific technology focus: developing methods for interactome analyses. We specialize in affinity proteomic approaches. Presently, we aim to translate our research tools, which explore and characterize protein interactions within multi-component macromolecular complexes, towards the clinic: for example, identifying differences in protein complex constituents between healthy and diseased patient tissues. Several projects in the lab seek to apply our interactome analytical tools to diverse biological questions, typically (but not exclusively) with connections to human diseases. The characterization of human LINE-1 retrotransposons is central among our biological interests. Over evolutionary time, LINE-1 sequences have come to compose a large proportion of the human genome and the latest studies suggest clinical implications for LINE-1 expression in e.g., cancer, autoimmunity, and neurodegeneration. We continue to explore the roles of LINE-1 in colorectal cancers and systemic lupus erythematosus. Most recently, we have initiated studies into the emerging connections between LINE-1 and Alzheimer's disease.

Macromolecules and Interactomes

John LaCava

Research Focus

Proteins and the multi-component macromolecular complexes they form are the effectors of cell biology. Studying cell biology therefore requires the ability to isolate distinct proteins along with other constituents of their associated macromolecules. Affinity proteomic techniques have greatly facilitated the discovery, purification, and characterization of endogenous protein complexes. These techniques leverage reagents able to target and capture proteins of interest assembled with physiological binding partners, from cell extracts. Although affinity capture has matured steadily as an approach, many technical shortcomings still limit its efficacy in the retrieval of intact, endogenous macromolecules. We address these challenges in affinity proteomics. We place special emphasis on approaches that also enable downstream structural and biochemical studies of enriched macromolecules. In the context of this technology focus, we are agnostic to the specific disease or underlying biology and collaborate widely on diverse projects with fundamental biologists and clinicians alike.

Long Interspersed Element 1 (LINE-1, L1), a retrotransposon, is a core biological interest of our lab. As a result of its “copy and paste” method of proliferation, L1 activity has contributed a large proportion of DNA to the human genome (including those sequences mobilized by L1, such as Alus). Since the insertion of new DNA sequences into the genome is inherently mutagenic, understanding the lifecycle of L1 is crucial to understanding human genome dynamics and cell biology. L1 DNA proliferates through an RNA intermediate whose protein products bind the L1 RNA to form a ribonucleoprotein (RNP) complex. L1 RNPs also co-opt and contend with a variety of host factors that facilitate or repress L1’s ability to reach the chromatin and reintegrate into the genome. Thus, different subpopulations of L1 RNPs consist of different assortments of constituents, depending on the cell type, subcellular compartment, and on the pathway being traversed (proliferation or repression). Our goal is to expand our breadth of knowledge concerning the L1 interactome, and we study the structural and biochemical properties of L1 RNPs, considering these interactions. In doing so, we also explore L1 contributions to pathobiology.

Macromolecules and Interactomes

John LaCava

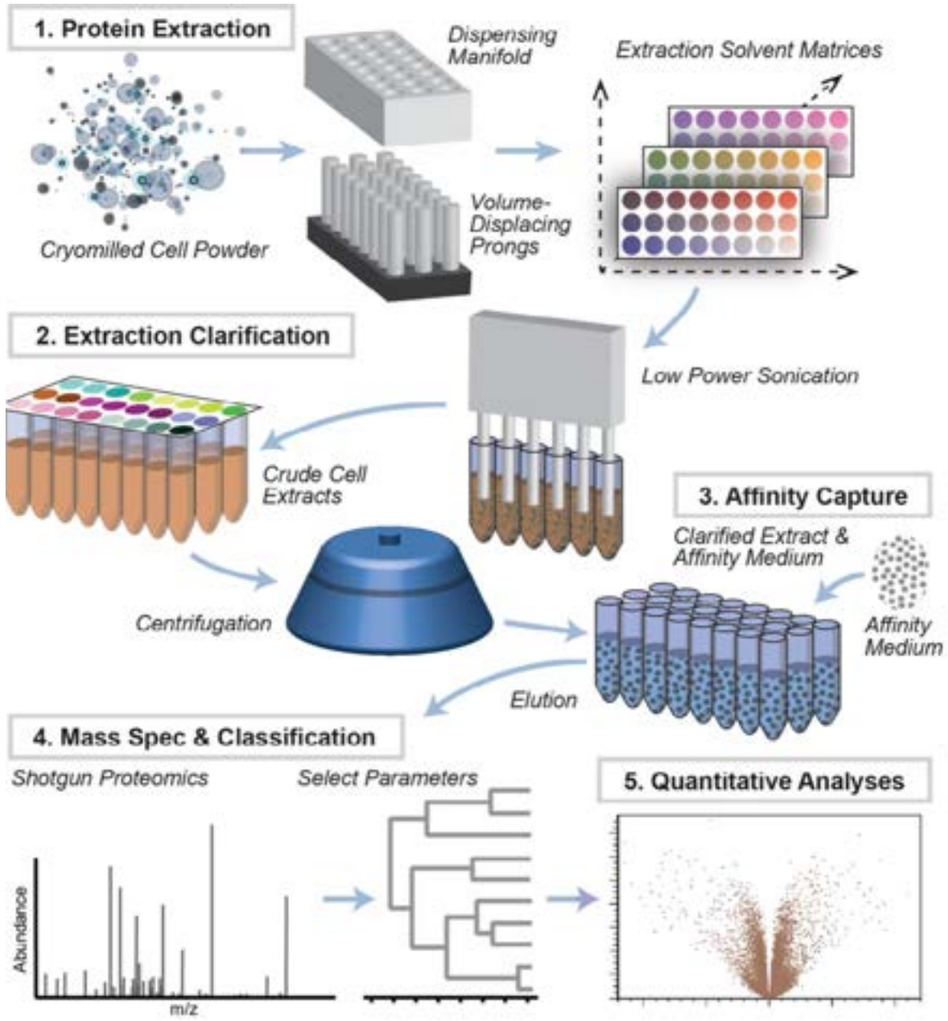

Figure.
Methodological approach. Cryomilled cell powders are distributed with a dispensing manifold and macromolecules are extracted with different extraction solutions (1). Brief sonication is applied to disperse and homogenize the extracts (2). After clarifying the extracts by centrifugation, affinity capture is performed (3) and protein eluates are subjected to MS analysis (4) and data processing

The Future

We are expanding our interactome charting approaches to include in situ proximity labeling. We will cross-reference macromolecular compositions defined by immunoprecipitation, which transfers macromolecules out of cells prior to identification, with those obtained by 'marking' the associating proteins while they still reside within cellular milieux. Taken together, the combination of these technique will provide complementary data to inform more comprehensive studies of protein complexes. We anticipate that proximity labeling may also allow us to make judicious use of FFPE tissue banks, whereas immunoprecipitation is carried out on fresh-frozen tissue, which is comparatively rare.

Our work with L1 is growing in numerous directions, chief among them, our development of a sensitive, quantitative biomarker assay for the detection of L1 ORF proteins in e.g., serum and cerebrospinal fluid. This assay is enabling us to explore diagnostic implications of L1 expression in cancers, autoimmunity, and neurodegeneration, which we are pursuing in on-going research.

Macromolecules and Interactomes

John LaCava

Selected Publication

Olivier JF, Langlais D, Jeyakumar T, Polyak MJ, Galarneau L, Cayrol R, Jiang H, Molloy KR, Xu G, Suzuki H, **LaCava J,** Gros P, Fodil N.
CCDC88B interacts with RASAL3 and ARHGEF2 and regulates dendritic cell function in neuroinflammation and colitis.
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doi: 10.1038/s42003-023-05751-9.
PMID: 38200184; PMCID: PMC10781698.

CCDC88B is a risk factor for several chronic inflammatory diseases in humans and its inactivation causes a migratory defect in DCs in mice. CCDC88B belongs to a family of cytoskeleton-associated scaffold proteins that feature protein:protein interaction domains. Here, we identified the Rho/Rac Guanine Nucleotide Exchange Factor 2 (ARHGEF2) and the RAS Protein Activator Like 3 (RASAL3) as CCDC88B physical and functional interactors. Mice defective in Arhgef2 or Rasal3 show dampened neuroinflammation, and display altered cellular response and susceptibility to colitis; ARHGEF2 maps to a human Chromosome 1 locus associated with susceptibility to IBD. Arhgef2 and Rasal3 mutant DCs show altered migration and motility in vitro, causing either reduced (Arhgef2) or enhanced (Rasal3) migratory properties. The CCDC88B/RASAL3/ARHGEF2 complex appears to regulate DCs migration by modulating activation of RHOA, with ARHGEF2 and RASAL3 acting in opposite regulatory fashions, providing a molecular mechanism for the involvement of these proteins in DCs immune functions.

Group Members

David Tabb Senior Staff scientist
Leila Saba Lab manager / Research technician
Mohammed Hanzala Kaniyar
Mass spectrometry research specialist
Nataliia Khoruzhenko Research technician
Omar Rosas Bringas PhD student
Apostolos Mourtzinos, PhD student
Ahmadresa Masoumi
GVO /non-paid PhD student

3. 2024: Highlights

This section reports a selected number of achievements that have been accomplished by ERIBA staff in 2024

Graduations

4 Students graduated from ERIBA last year.

Sara Mouton	Liesbeth Veenhoff
Siqi Zheng	Floris Foijer
Katya Dvorianinova	Floris Foijer
Natalia Skinder	Gerald de Haan

Grants

ERIBA scientists were awarded with various prestigious grants.

The total funding for 2024 was

2.8 million euros

Publications

In 2024 ERIBA scientists published

66 papers

ERIBA

4. Valedictory address by the Managing Director

ERIBA
the challenge

Slowly moving to my retirement age it is always a nice moment to reflect, to look back on your career or on a specific assignment. For me building up a new institute was such a nice and new challenge. At that time the department manager in the Genetics department a meeting with one of the Board members on the fish-market was the start of that challenge. The follow up was a meeting with the Board where the new strategic focus was explained and the two major projects for UMCG, ERIBA and lifelines were ready to be kicked off. After my “Yes” we had a flying start, converted the business plan into a project plan where we four issues to tackle. First we had to construct a new building. We had to fill this building with equipment and furniture, for which we needed quite some European tenders, we had to build a new UMCG organization, known in all the UMCG systems and of course we had to recruit researchers, fill their teams and give them a kick start.

The combination Rudy Uytenhaak/ Friso bouw constructed a brand new building, also in a brand new design, based on shared facilities (labs) and open office. They created a working environment with a lot of light and air that invites to share knowledge and new ideas. The first researchers started in November and December 2011. As there was no building yet, they started at Zernike and in other labs within UMCG. In June 2012 the building was ready for the big move and the first groups started in the ERIBA building. Of course there were quite some starting issues that gave the research groups down time in their project. In 2013 we had the official start of ERIBA with a nice opening event.

We write 2024 now and last year we had our 10 year anniversary. Since the start we had a lot of achievements. With the 13 research groups we have a total population of 81 people that work in ERIBA. The researchers produced in these 10 years 530 papers and 59 PhD students defended their thesis. In total we were able to realize a funding sum of € 30.95 mln. Figures we can really be proud of. We are the international ageing Institute well known all over the world.

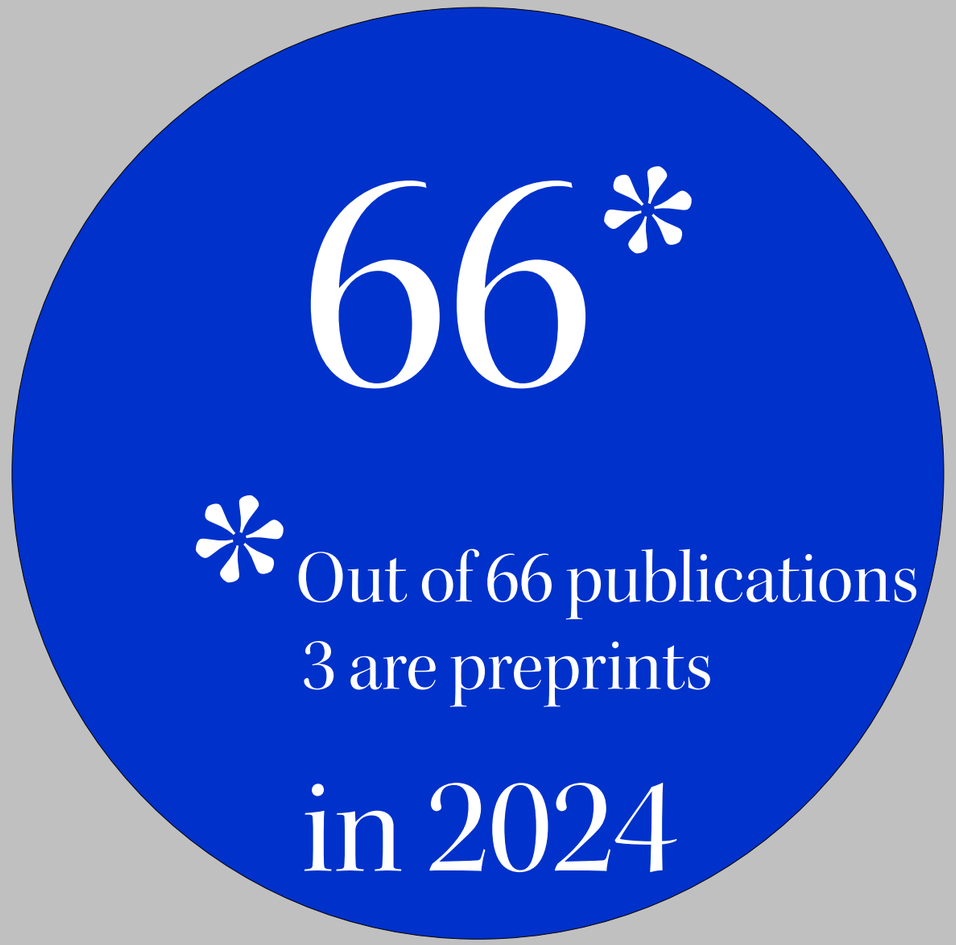
But we are not yet there. The building can accommodate double the amount of people, so yes there is potential to grow. We have new challenges. The funding situation in the Netherlands doesn't help to realize all new research ideas. So we need to be creative in finding the money to keep the innovation motor moving. We still need to do a lot of effort to attract people from all over the world to come to Groningen. Also in UMCG as a company we encounter some challenges, which will have its effects on ERIBA.
So yeah almost retiring, but is the job done? For sure not. There are some issues to do…. But for my successor: it is such a nice task to work with all these passionate professionals, driven by curiosity, drive for the research and education, drive to bring the science to business. To contribute to such a wonderful institute is a dream for every manager. I loved it and I hope ERIBA will expand in the future and will bring a lot of new findings to the world.

Henk Heidekamp

Managing Director

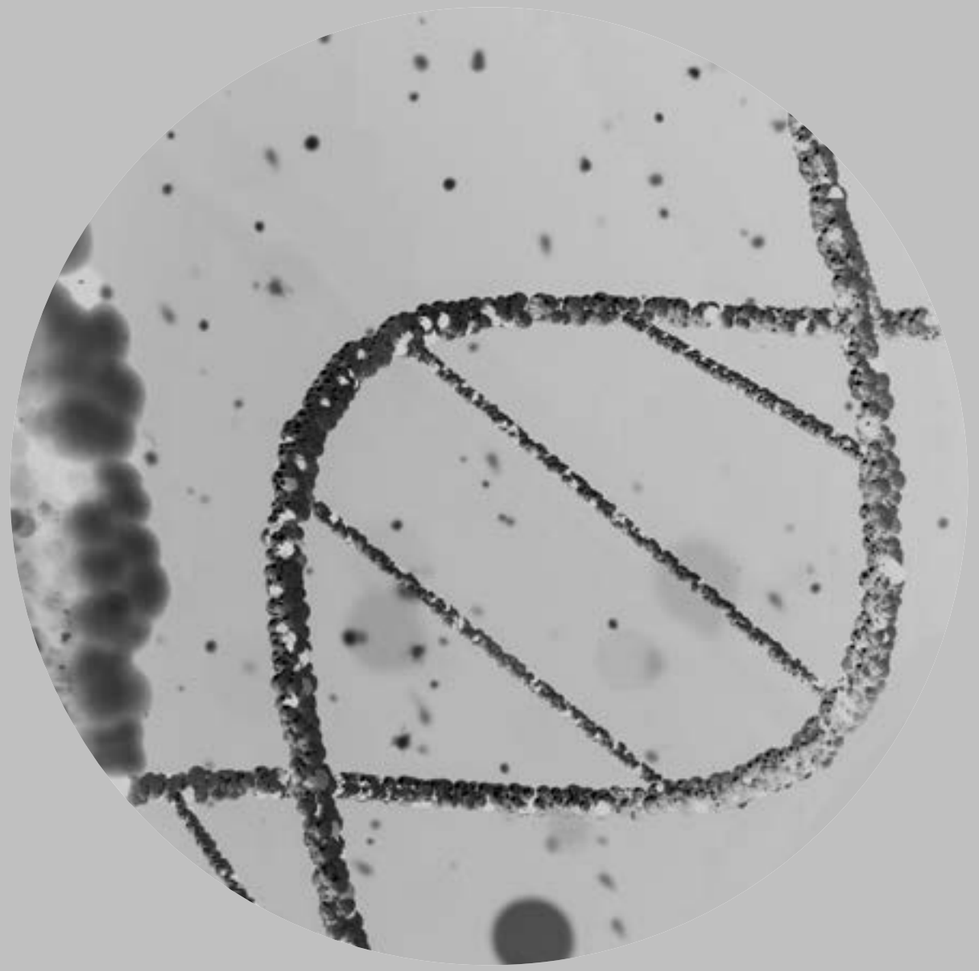
5. Facts and Figures

Scientific Publications



Laboratory of Gene Regulation in Ageing and Age-Related Diseases

Cor Calkhoven



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Sequencing Facility

Diana Spierings

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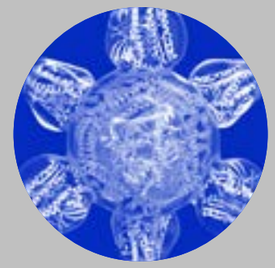

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Laboratory of Molecular Neurobiology of Ageing

Ellen Nollen

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Eugene Berezikov

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Laboratory of Gut-Liver Axis in Healthy Ageing

Folkert Kuipers

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Folkert Kuipers

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Laboratory of Gut-Liver Axis in Healthy Ageing

Folkert Kuipers

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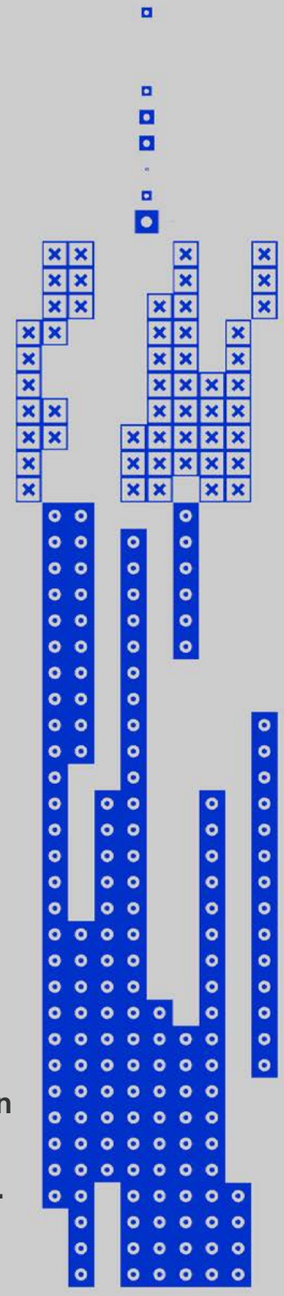

Laboratory of Macromolecules and Interactomes

John LaCava

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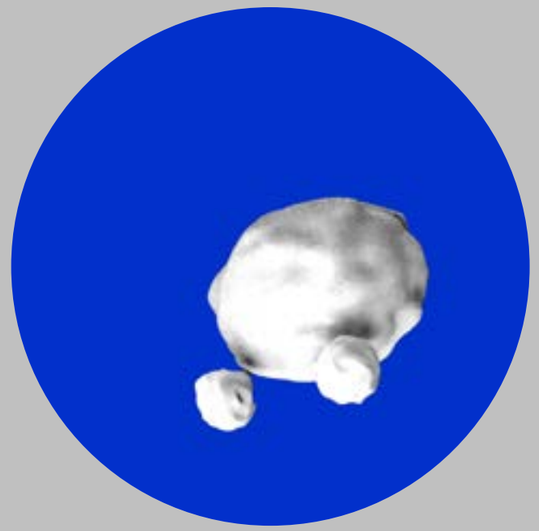

Laboratory of Macromolecules and Interactomes

John LaCava

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Laboratory of Asymmetric Cell Division and Ageing

Judith Paridaen

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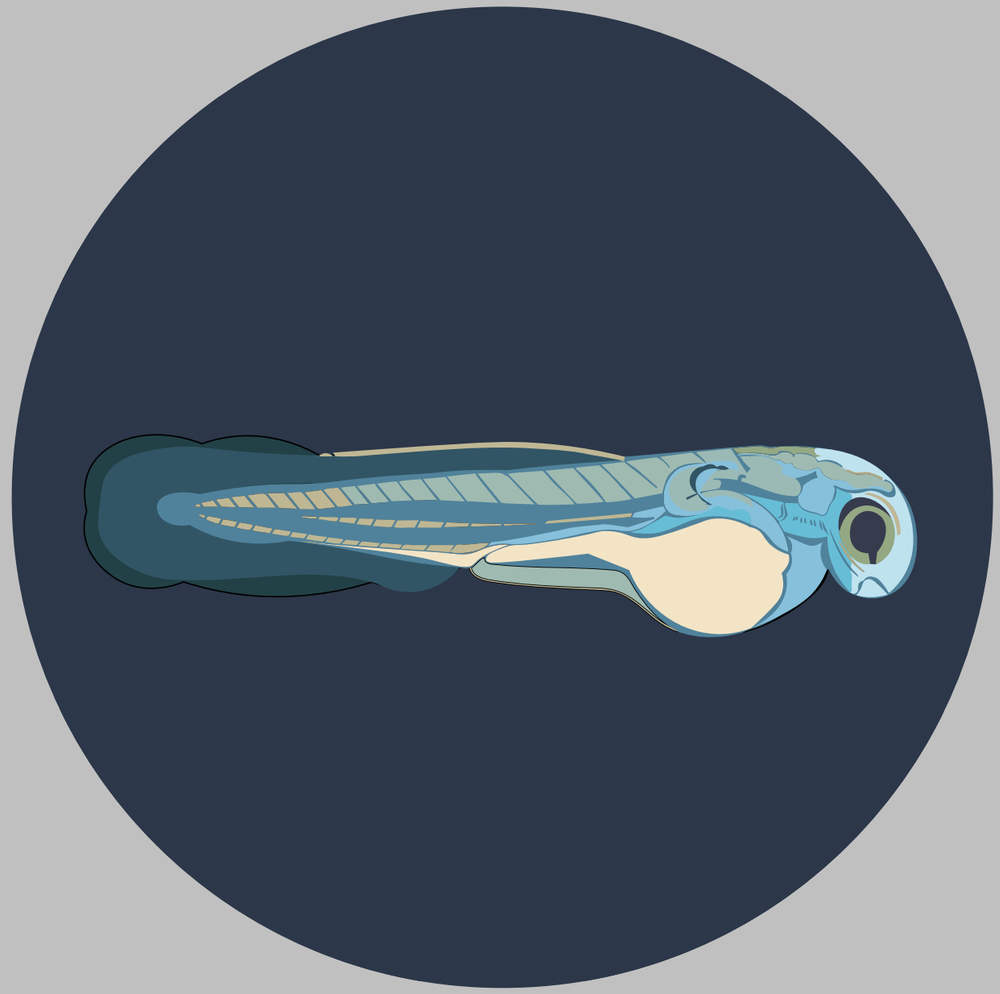
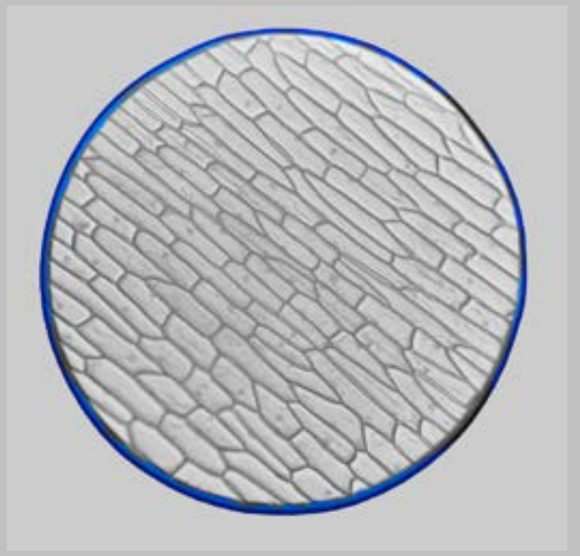


Laboratory of Cellular Biochemistry

Liesbeth Veenhoff



Microscopic image by *Ash Hayes*

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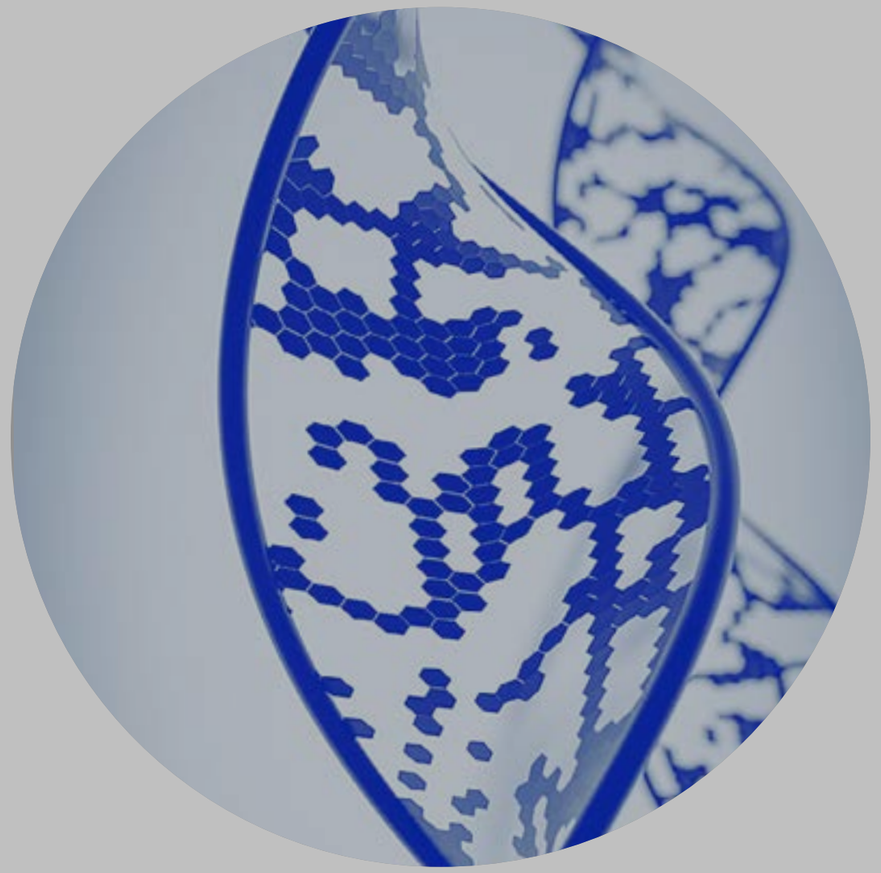
Laboratory of Cellular Biochemistry

Liesbeth Veenhoff



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Laboratory of Cellular Senescence and Age-Related Pathologies

Marco Demaria

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Laboratory of Cellular Senescence and Age-Related Pathologies

Marco Demaria

Venz R, Goyala A, Soto-Gamez A, Yenice T, **Demaria M**, Ewald CY.
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Epub 2023 Dec 4.

Laboratory of Telomeres and Genome Integrity

Michael Chang

Yao Y, Yin Z, Rosas Bringas FR, Boudeman J, Novarina D, **Chang M. Revisiting the role of the spindle assembly checkpoint in the formation of gross chromosomal rearrangements in Saccharomyces cerevisiae**. Genetics. 2024 Sep 12:iyae150. doi: 10.1093/genetics/iyae150. Epub ahead of print. PMID: 39268895.

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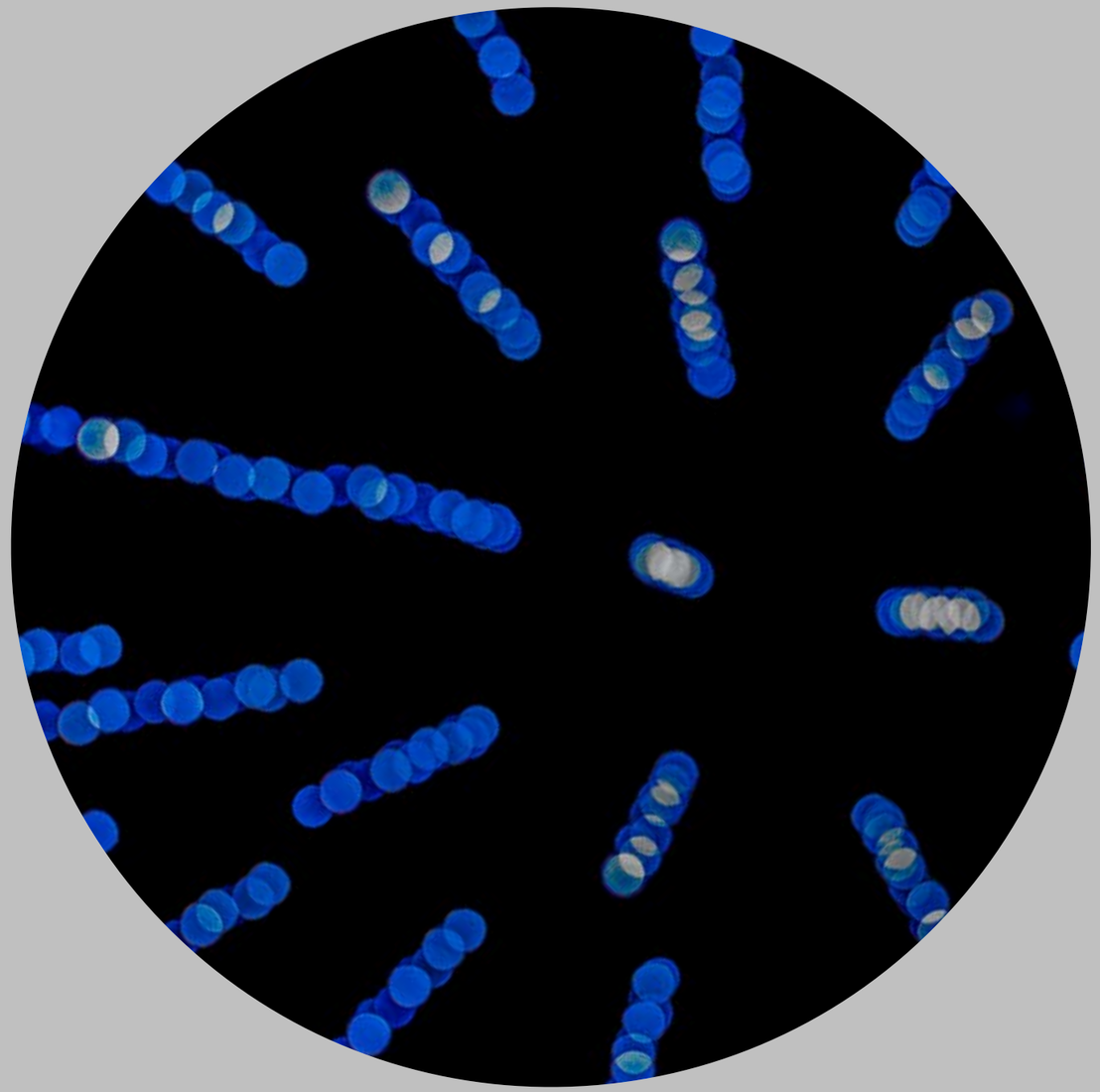
Photo by Kajetan Sumila



Laboratory of Genome Structure Ageing

Victor Guryev

Khalenkow D, Brandsma CA, Timens W, Choy DF, Grimbaldeston MA, Rosenberger CM, Slebos DJ, Kerstjens HAM, Faiz A, Koppelman GH, Nawijn MC, van den Berge M, **Guryev V**. (2024) **Alternative Splicing Is a Major Factor Shaping Transcriptome Diversity in Mild and Severe COPD**. Am J Respir Cell Mol Biol. Epub ahead of print.

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Laboratory of Genome Structure Ageing

Victor Guryev

de Jong TV, Pan Y, Rastas P, Munro D, Tutaj M, Akil H, Benner C, Chen D, Chitre AS, Chow W, Colonna V, Dalgard CL, Demos WM, Doris PA, Garrison E, Geurts AM, Gunturkun HM, **Guryev V**, Hourlier T, Howe K, Huang J, Kalbfleisch T, Kim P, Li L, Mahaffey S, Martin FJ, Mohammadi P, Ozel AB, Polesskaya O, Pravenec M, Prins P, Sebat J, Smith JR, Solberg Woods LC, Tabakoff B, Tracey A, Uliano-Silva M, Villani F, Wang H, Sharp BM, Telese F, Jiang Z, Saba L, Wang X, Murphy TD, Palmer AA, Kwitek AE, Dwinell MR, Williams RW, Li JZ, Chen H.
A revamped rat reference genome improves the discovery of genetic diversity in laboratory rats.
Cell Genom. 2024 Apr 10;4(4):100527.
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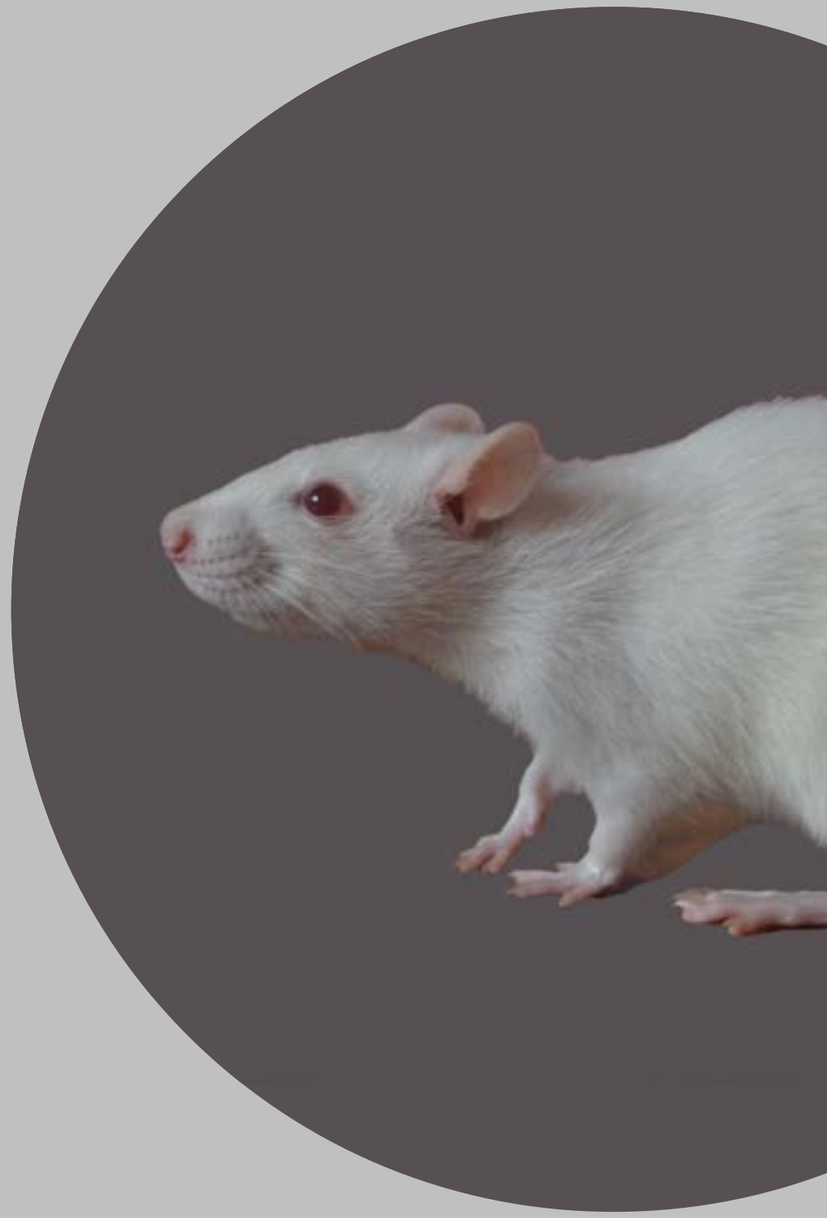
Epub 2024 Mar 26. PMID: 38537634; PMCID: PMC11019364.



Funding/ Grants

€ 2,832,601.00

Total funding for projects started during 2024

Funding/Grants

Researcher	Call	Title of the project	Amount
Cor Calkhoven **Clément Karch**	De Cock-Hadders Foundation funding for scientific research	A dual-fluorescence translation-reporter system to study oncogenic expression of C/EBP	€ 4,600.00
Ellen Nollen **Lale Güngördü**	The ALS Foundation Netherlands	8 ChannALS: Rebalancing neurotransmission in ALS by targeting ion channels	€ 356,000.00
Eugene Berezikov	NWO-XS	An ultimate approach for analysing complete transcriptomes, from bulk samples to single cells	€ 50,000.00
Stijn Mouton Eugene Berezikov's Group	NWO-XS	In search of a Super Hero Protein	€ 50,000.00
Ellen Nollen	HORIZON-WIDERA-2023-ACCESS-02-01-Twinning Bottom-Up	TWIN4EarLiStAge : Twinning for excellence in Research, training and innovation in early-in life stress and aging.	€ 284,406.00
Marco Demaria	Hevolution Foundation	Characterization of sexual dimorphism in ageassociated cellular senescence	€ 1,379,954.00
Michael Chang	Campagneteam Huntington	Identifying genetic regulators of CAG repeat stability	€ 50,000.00
Liesbeth Veenhoff	Campagneteam Huntington	Is phase state regulation a relevant strategy to stabilize less toxic forms of Huntingtin?	€ 50,000.00
Ellen Nollen	Parkinson Fonds	Understanding how lipid metabolism contributes to	€ 224,000.00
Floris Foijer	NWO-XS	Establishing a zebrafish model to monitor chromosome missegregation events in vivo	€ 50,000.00
Van den Brink Floris Foijer's Group	De Cock-Hadders Foundation funding for scientific research	Cell-intrinsic inflammatory signaling: a selective targetable driver of tumors with chromosomal instability?	€ 4,600.00

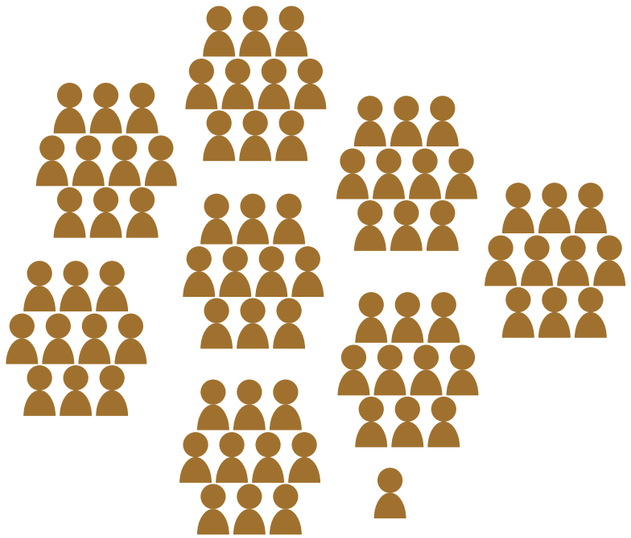
Funding/Grants

Researcher	Call	Title of the project	Amount
Karina Köpke Floris Foijer's Group	De Cock-Hadders Foundation funding for scientific research	Investigating the role of extracellular matrix stiffness in glioblastoma in an orthotopic zebrafish model	€ 4,600.00
Xiao Ling Floris Foijer's Group	De Cock-Hadders Foundation funding for scientific research	How does inflammation affect treatment efficacy in chromosomal instability cancer	€ 4,600.00
Siburian Floris Floris Foijer's Group	De Cock-Hadders Foundation funding for scientific research	Study on Cancer-Immune Interaction during Carcinogenesis and Cancer Progression using Breast Cancer Organoid Model	€ 4,600.00
Abdullah Altulea Marco Demaria's Group	De Cock-Hadders Foundation funding for scientific research	Differentiating between beneficial and detrimental senescence.	€ 1,500.00
Yao Lin Marco Demaria's Group	De Cock-Hadders Foundation funding for scientific research	a multi-omic approach reveals sex-dependent metabolic r ewiring in aged tissues after senolysis	€ 4,600.00
Teodora Gheorghe Marco Demaria's Group	De Cock-Hadders Foundation funding for scientific research	Repurposing calcium channel blockers as novel senolytics	€ 4,600.00
Suzzane Couzijn Ellen Nollen's Group	De Cock-Hadders Foundation funding for scientific research	Biological mechanisms of age-related	€ 4,541.00
Anna Ainslie Ellen Nollen's Group	Alzheimer Nederland	Arming neurons against ageing and dementia: Elucidating neuroprotective mechanisms of neuronal circuits in C. elegans models of ageing and dementia	€ 300,000.00

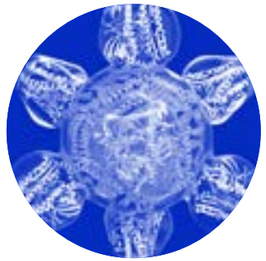
Total funding for projects started during 2024 **€ 2,832,601.00**

People

Staff Members



Total
employees
81



People

Dutch employees

48

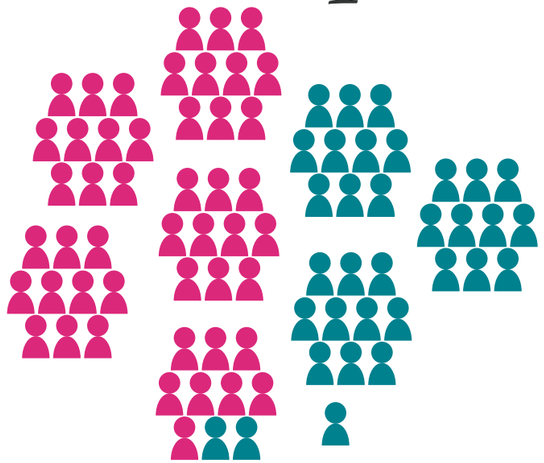
International employees

33

Total Nationalities

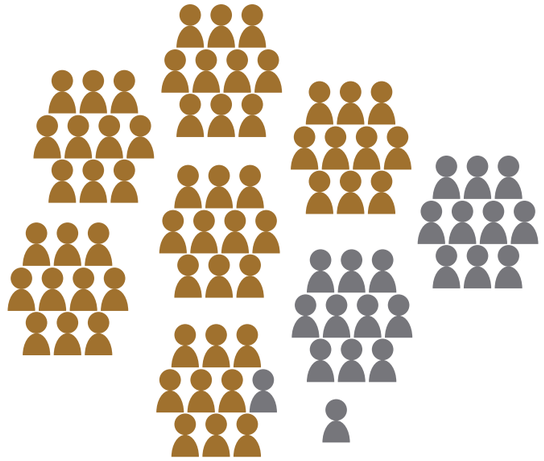
33

People



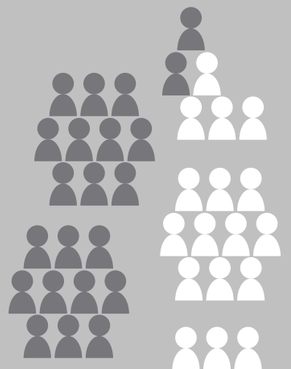
Number of Women
48

Number of Men
33



ERIBA
PhD Students
22

Other employees
59

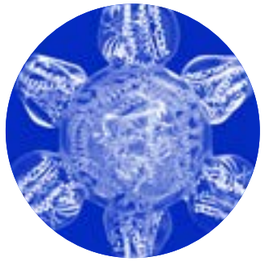


PhD Students in Total
46

ERIBA
PhD Students
22

PhD Students with scholarship
24

Management Team



Folkert Kuipers	Scientific Director
Henk Heidekamp	Managing Director
Jesse Medema	Finance Project Controller
Megha Upadhyay	Research Coordinator
Ria Ubels	Staff Advisor
Sylvia Hoks	Secretary
Karin van Wageningen	Secretary
Joke Eleveld	Secretary
Yin Fai Chan	Technician (General Support)

Invited Speakers

INVITED SPEAKER	INSTITUTION	TITLE OF THE TALK	EVENT
Anna Malkova	UT Health San Antonio, Texas, USA	Break-induced replication: The mechanism and its role in telomere lengthening	ERIBA lecture
Klaske Schukken	Yale School of Medicine, USA		ERIBA Friday Seminar
Marcel Tijsterman	LUMC	The Good, the Bad and the Ugly in repair of Chromosomal Breaks	ERIBA Friday Seminar
George Garinis	University of Crete, Greece.	DNA damage and Innate Immune Responses during Aging	ERIBA/Mol Med Series
Jan Vijg	Albert Einstein College of Medicine in New York, USA	Somatic mutations and aging: cause or effect?	ERIBA lecture
Brandon Peterson	Biomaterials and Biomedical Technology, RUG, The Netherlands	Bacterial Adadtability - a form of intelligence'	ERIBA Friday Seminar
Myriam Gorospe	National Institute of Health, Baltimore, USA	Insights from Senescence into Age-Associated Neurodegeneration	ERIBA/Mol Med Series
Xiangli Bian	GemPharmatech	Genetically Modified Mouse Models and Applications	ERIBA lecture
Trevor van Eeuwen	Rockefeller University NY, USA.	Structural analysis and inhibition of human LINE-1 ORF2 protein reveals novel adaptation and functions	ERIBA/Mol Med Series
Zhao Zhang	Duke University, Durham, USA	Chasing the jumping genes: from ecDNA biogenesis to cancer immunotherapy	ERIBA/Mol Med Series
Barbara Bakker	Pediatrics, UMCG	Didgital Twins: towards a personalised systems medicine approach for metabolic disease	ERIBA Friday Seminar
Herman Sillje	Head Experimental Cardiology Laboratory, RUG	Mouse Studies Illuminate Disease Mechanisms and Therapeutic Approaches in Phospholamban Cardiomyopathy	ERIBA Friday Seminar
Andromachi Pouikli	CECAD/Max Planck Institute for Biology of Ageing	The mito-nuclear communication in ageing and cancer	ERIBA lecture
Peter van der Meer	UMCG, The Netherlands	Translational tools to improve personalized treatment in heart failure	ERIBA Friday Seminar

6. Facilities

Functional Genomics Centre iPSC/CRISPR facility

The discovery of protocols to reprogram somatic cells into induced pluripotent stem cells (iPSCs) is revolutionizing regenerative medicine. The therapeutic promise of iPSC technology includes the production of isogenic cell lineages and (in the future) tissues to replace body parts that can be autografted in patients when organs are failing. Importantly, when combined with CRISPR genome engineering technology, iPSC technology can be used to cure (mono) genetic diseases, by repairing the disease-causing mutation in patient-derived iPSCs and by differentiating the repaired cells into functional tissues and transplanting them back into the patient.

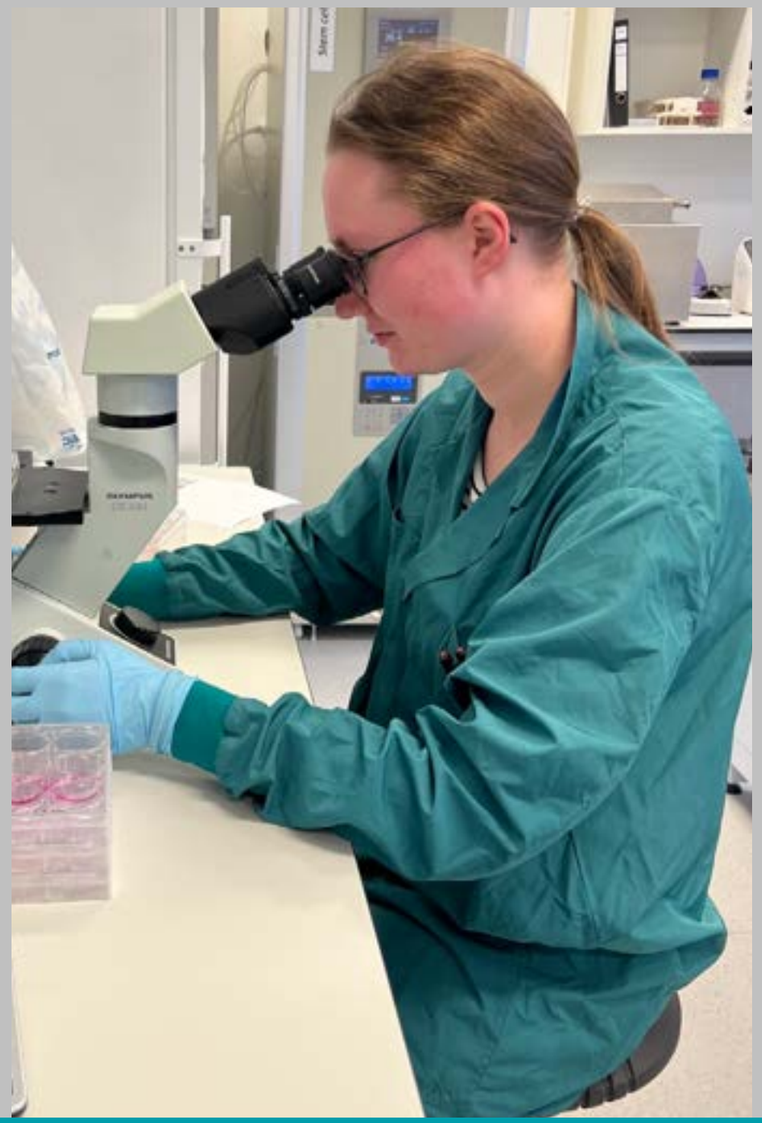
The iPSC/CRISPR centre at ERIBA aims to contribute to this therapeutic promise. For this, we help UMCG and RUG employees with deriving iPSCs and establishing differentiated cultures from these iPSCs. Furthermore, we help our customers with CRISPR genome engineering, including making knockout cell lines, engineering point mutations, tagging endogenous genes, etc. in various cell lines, including iPSCs. In addition, we facilitate genome-wide CRISPR functional screens and together with the Netherlands Cancer Institute and Leiden University we form a national KWF-funded CRISPR screen infrastructure – ScreeninC - supporting CRISPR screens at the national level. Our role in this consortium is to develop CRISPR-screens in complex model systems such as organoids (in collaboration with Jarno Drost at the Princess Maxima Centre), in iPSCs, and in mice (in collaboration with Bart van de Sluis, UMCG)

Since the start of the center in 2016, we accommodated >130 different projects for more than 60 different groups. As part of these projects, we implemented a number of differentiation protocols and protocols to grow cerebral organoids. In addition to supporting 'standard' CRISPR KO services, we also implemented protocols to genome-engineer tags onto genomic loci and introduce point mutations of choice into various cell lines, including iPSCs. So far, we supported/are supporting more than 10 CRISPR screens since the start of the KWF-funded ScreeninC consortium. While we support all types of CRISPR screens (including CRISPRa and CRISPRi), our current development goals are to implement and validate 'complex' CRISP screens such as screens in iPSCs, organoids or in mice. For the latter, we are, together with Bart van der Sluis, performing a somatic CRISPR screen in liver to identify modulators of liver cancer. We expect that support of CRISPR screens will remain an important task for our team in the coming years.

Importantly, we regularly host MSc students for internships and we each year we organize the CRISPR genome engineering course for Biomedical Sciences MSc students, the JSM course 'Model systems in ageing research' for third year medical students and host medical students for the BSc theses. Importantly, we trained many PhD students and postdocs in deriving and maintaining iPSCs and in differentiating iPSCs into various cell types.

As of 2020, our center's funding was renewed for another 5 years. Last year, we successfully implemented a tissue culture robot to automate iPSC reprogramming in our iPSC generation pipeline, which drastically improves our iPSC line generation capacity. In its first operational year (2023), the robot helped us to reprogram ~50 lines, which doubled our reprogramming capacity. We expect to double our capacity at least once more in the next 2 years. We are closely involved with the AgeingLines cohort study and in collaboration with Debby van Baarle (UMCG), we ensure that PBMCs for all AgeingLines participants will be collected and stored so that we can generate iPSCs from deeply phenotyped AgeingLines participants in the years to come.

As our funding is running out next year (end of 2025), the Research Sequencing Facility and Functional Genomics Center teams up in an application for PharmaNL, a Netherlands Growth Fund initiative that is meant to support research infrastructures that support drug discovery and drug availability in the Netherlands. This application yielded a € 5.7 million grant that allows us to establish a company that will commercialize the services of both ERIBA facilities. The resulting company – iPsomics – was established in October 2024 and will take over all ERIBA research facilities activities. The aim is to become financially sustainable in the next five years by development of new applications of our technology, by establishing a portfolio of loyal customers (academic and commercial) and by ensuring sufficient commercial income to keep the academic prices as close to cost price as possible. iPsomics current key products include single cell phenotyped iPSC-derived disease models (including organ on a chip models in collaboration with Sebo Withof, Dpt. Genetics) and single cell sequencing powered diagnostics to improve cancer patient and treatment stratification. iPsomics is a UMCG-owned business with three directors: Peter Keterlaar, CEO, Henk Heidekamp, CFO and Floris Foijer (CSO) and will employ all ERIBA facilities personnel from 2025 onward as well as two more technicians and a project manager located at the Department of Genetics.



Who

Floris Foijer
Coordinator Functional Genomics Centre

Mathilde Broekhuis
Lab manager

Petra L. Bakker
Project manager

Marilucrezia Losito
Postdoctoral fellow

Laura Kempe
Research technician

René Wardenaar
Bioinformatician

Contact from 2025 onward

iPsomics
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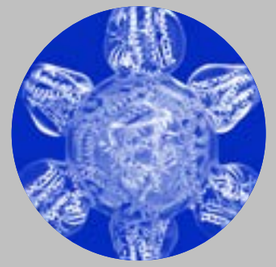
Internal Zip Code FA50
9700AD Groningen

Marialucrezia Losito
project manager iPsomics
m.losito@umcg.nl

Peter Ketelaar
CEO iPsomics
peter.ketelaar@ipsomics.com

Floris Foijer
CSO iPsomics
f.foijer@umcg.nl; floris.foijer@ipsomics.com

Sequencing Facility

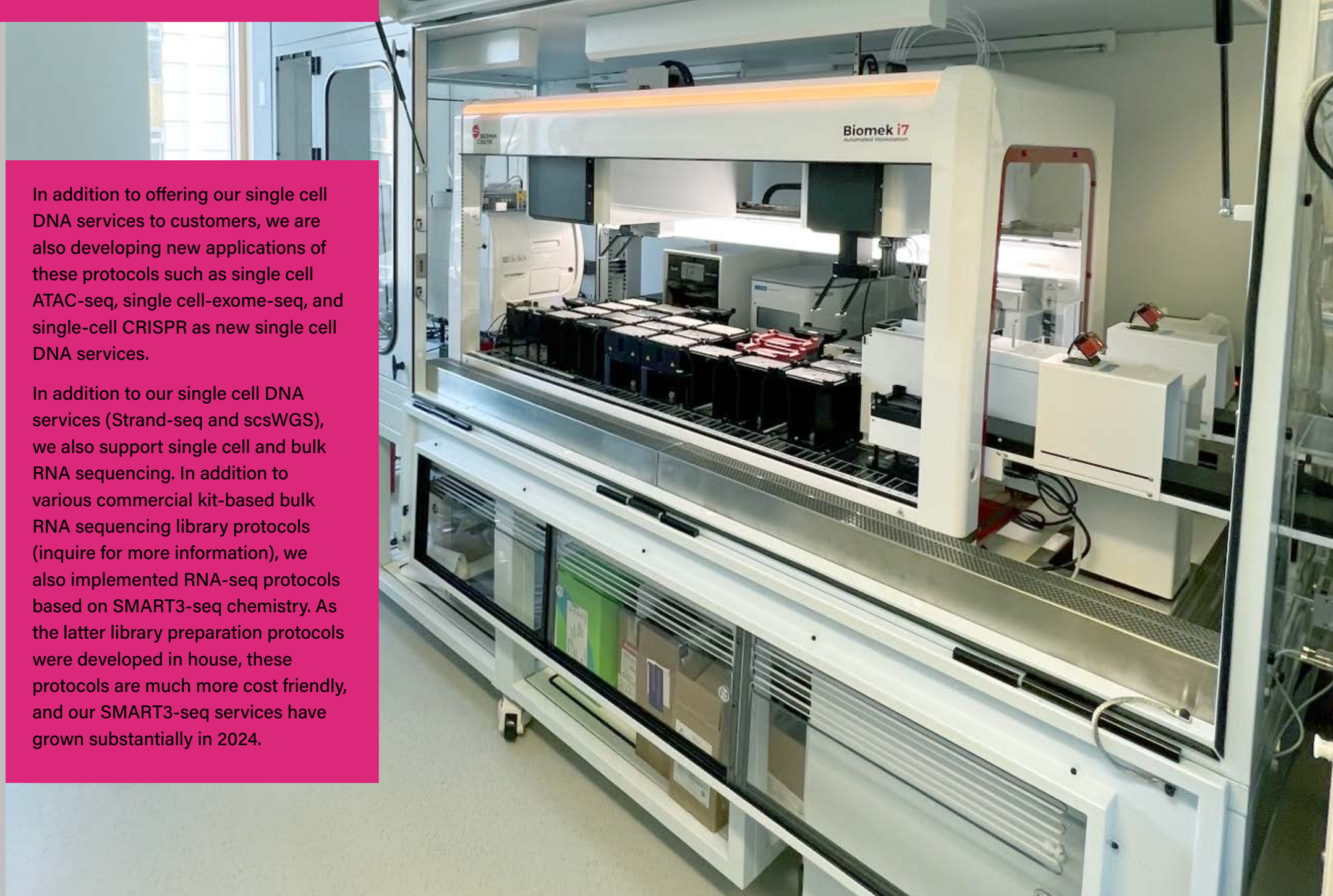


Next generation sequencing (NGS) technology is revolutionizing medicine and life sciences and has become a routine tool to assess the genomes, epigenomes and transcriptomes of cultured cells, (liquid) biopsies, and primary tissue/disease samples.

In May 2019, the Research Sequencing Facility was officially established within the ERIBA Technology Center, as a dedicated research infrastructure to provide support for NGS-based projects for UMCG and RUG research groups. For this, we will not only facilitate the expeditious sequencing of NGS libraries either prepared by research groups themselves or by the facility on behalf of the researcher, but also implement the latest NGS techniques used in medicine and life sciences research, and (co)develop and implement new state-of-the-art NGS techniques to keep NGS-dependent research in the UMCG at the forefront. Furthermore, we advise the researchers on the set-up of their NGS experiments and train researchers in the production of NGS libraries if they would prefer to do this themselves. As a spinoff of the former Peter Lansdorp lab and in close collaboration with the Foijer lab, our facility became a world leading service provider for shallow single-cell whole genome sequencing (sscWGS) with many external customers approaching us to characterize karyotype variability within primary tumor samples and cell cultures. In addition to scsWGS, we also offer STRAND-seq, an advanced single cell whole genome sequencing application through which we can detect inversions and translocations by assessing single DNA molecule strand direction. We continuously improve our protocols and in 2024 we made substantial progress with the implementation of a lower cost protocol for scsWGS that reduces the cost price by ~60% and increased the throughput four fold. We will continue the further improve the platform as part of the newly established company iPsomics in the coming years (also see below).

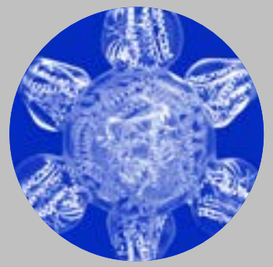
In addition to offering our single cell DNA services to customers, we are also developing new applications of these protocols such as single cell ATAC-seq, single cell-exome-seq, and single-cell CRISPR as new single cell DNA services.

In addition to our single cell DNA services (Strand-seq and scsWGS), we also support single cell and bulk RNA sequencing. In addition to various commercial kit-based bulk RNA sequencing library protocols (inquire for more information), we also implemented RNA-seq protocols based on SMART3-seq chemistry. As the latter library preparation protocols were developed in house, these protocols are much more cost friendly, and our SMART3-seq services have grown substantially in 2024.



For single cell RNA sequencing, we have mostly made use of the commercial 10X Genomics platform. At the end of 2023, we purchased a lower cost alternative of this platform (Seekgene), which has now fully been validated and implemented. In addition to implementing a Seekgene pipeline, we are also developing our own SMART3-seq-based scRNA pipline, which we hope to implement in 2025.

As described in more detail under the Functional Genomics Center, both ERIBA facilities will continue as a PharmaNL-funded newly established company – iPsomics. iPsomics will continue to offer the services that were offered by the Research Sequencing facility and furthermore develop new applications that build upon our current pipelines. Although we need to become fully self-sustainable in the next 5 years, we expect that our academic prices will stay competitive or even decrease as we have implemented and are developing lower cost pipelines for many to most of our services. This guarantees a continuation of our services while at the same time being more cost effective.



Who

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Floris Foijer
Interim coordinator sscWGS services

Diana Spierings
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7. Education

ERIBA scientists participate in a wide range of educational activities. Here is a selection of their significant contributions to teaching, not including the many individual lectures and undergraduate student internships.

Molecular Biology of Ageing and Age-related diseases

20 students, 5ECTS

Coordinators

Liesbeth Veenhoff
Michael Chang co-coordinator

Objective

Ageing can be defined as the gradual loss of the ability of the organism to maintain homeostasis. In this course we focus on the molecular and cellular mechanisms by which tissue and organ function deteriorate and homeostasis fails, resulting in ageing and age related disease. We will evaluate to what extent the up-to date knowledge on the molecular biology provides opportunities for interventions, also when considering what we learn from evolutionary theories of ageing. We present the model systems and experimental strategies that are used in ageing research. This course will be supported by a team of specialists in different fields of ageing that will provide lectures and reading material. The course not only gives an overview of the research field of ageing but also teaches scientific writing, active listening and giving feedback.

MMIT - Experimental techniques in research

28 students 10ECTS

Coordinators

Michael Chang and
Liesbeth Veenhoff

Objective

Week 1 will be an introduction week on basic research skills in which the students will learn basic programming, statistics, graphing and designing experiments. Weeks 2-6 will provide an overview of state-of-the-art techniques in several areas of biomedical- and pharmaceutical research, including genomics, animal models, imaging, protein research, and translational research. Established researchers will introduce these techniques and present their current research to demonstrate how these techniques can be used to answer a specific research question. Each week, you will work on an assignment, which will finish on Friday with a presentation or other type of evaluation. In week 7 students are assigned a specific genetic disease to study. The average grade of these weekly assignments will constitute the final grade for this course.

Track on biology of healthy ageing and disease (programme) MSc CRISPR

30 students 5 ECTS

Coordinators

Kai Yu Ma Genetics;
Floris Foijer Lab training Coordinator (ERIBA)

Objectives

In this course, MSc learn the basics of CRISPR engineering. Students learn about the history and various applications of CRISPR including knockouts, knockins,CRISPR I, CRISPRa, mutations and genome-wide screens. Furthermore, they get hands-on experience in the designof guide RNAs and genome editing tools and apply them in the lab. Finally, they combine their newly acquired expertise in an assignment in which they design a complete CRISPR strategy for a fictive project.

Model organisms in ageing research course

10 students 3 ECTS (JSM BSc course)

Coordinator

Floris Foijer ERIBA

Objectives

In this JSM course, third year medical students explore fundamental biology and are exposed to several of the model organisms we use at ERIBA for ageing-related research. Students discuss advantages and disadvantages of the model organisms with researchers on the lab. and study relevant papers that make use of the model organisms. In small groups, they compare the feasibility of 2-3 models Ito study (aspects of) a particular disease and discuss the advantages and disadvantages of these models in this setting.

Biology of Ageing for PhD students

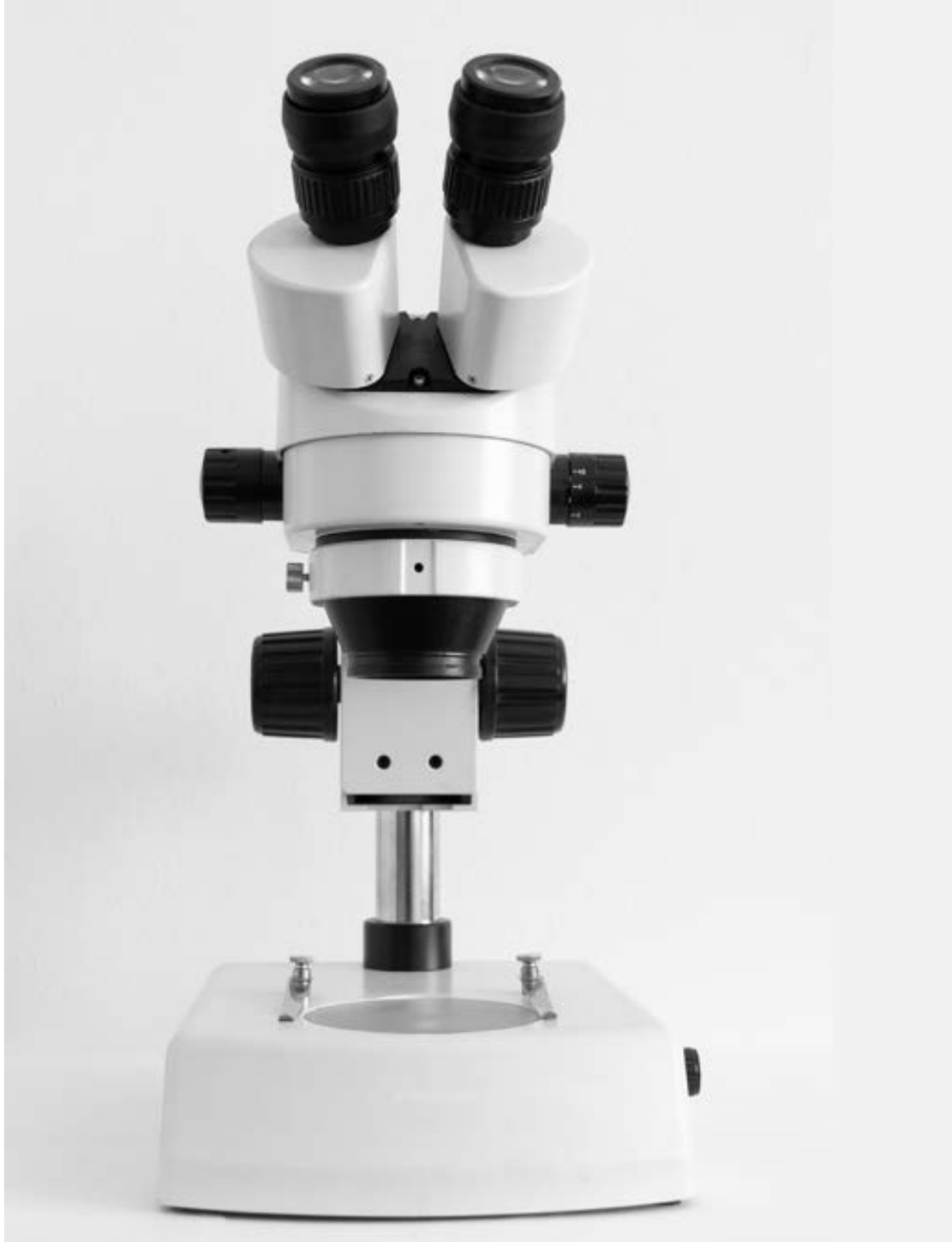
8 Students 1 ECTS

Coordinators

Marco Demaria and
Judith Paridaen

Objective

The ERIBA organizes a course for all our first-year PhD students. The course consists in 1 lecture/ month where an ERIBA PI will talk about her/his research and perspectives in the field. The course is highly interactive, and discussion is mandatory. In addition to first-year students, we highly encourage all the students that did not participate a previous edition of the course to do so.



Data science in biomedicine

~100 MSc students, 5 ECTS

Coordinators

Victor Guryev
Anne de Jong
Jaap Broos

Objective

Biomedical sciences is a fast evolving multidisciplinary research knowledge field in which new disciplines, like bioinformatics, machine learning and artificial intelligence have advanced rapidly during recent years. This course offers students an introduction into: computational biology, programming and big-data management. Students will be trained to: mine for genetic diseases in international databases, analyze and visualize transcriptome data, read and edit programs and visualize their results in R. This course prepares the master students for the FSE/FMW learning line “Datascience”.

Age Research ERIBA Course 2024

14 students, 10 ECTS

Coordinator

Cor Calkhoven

Objective

The Bachelor’s research project, combined with the Bachelor’s thesis, forms the last phase of your Bachelor’s degree programme. By the end of the research period, students (supervised by a lecturer) must show that they are able to use the knowledge and skills they have acquired throughout the programme in concrete practical/research situations and that they are able to report their activities and findings in an academic fashion. The Bachelor’s research project can also help students to find the right Master’s programme.

The Bachelor’s research project comprises an independent research/design project within the student’s chosen Major, and is rounded off with an individual written report (research report) and a final oral presentation.

8. Public Outreach & Dissemination

ERIBA scientists and
the outreach committee
is engaged in various
public outreach activities.
Here are some events
organized in 2024

Date 05-10-2024

Zpannend Zernike

~1025 visitors.

There were 15 stands/ activities. We as ERIBA worked together with Genetics and Paediatrics department. Various activities were organised for the school kids such as: DNA from banana, microscopy, dress up as scientist, escape rooms. For more details you can check the website:

www.ZpannendZernike.nl

Date 18-12-2024

School Visit

We have welcomed a group of 24 children from the 5th class from Waskemeer. We organized a small presentation with three activities; Microscopes (worms and fishes), pipetting on the lab and the escape room.

Science in a box

Leading Staff Member **Stijn Mouton**

In 2019, “Science in a Box” was officially ,launched, and the first “Regeneration Boxes” were sold. These boxes provide a hands on experience to explore topics such as regeneration and stem cells in the class room. Hanze University has included these boxes in their curriculum.

9. Scientific Advisory Board

Christine Mummery

Professor of Developmental Biology

Chair of the Department of Anatomy and Embryology

Leiden University Medical Center

The Netherlands

Helle Ulrich

Executive Director of the Institute of Molecular Biology

Professor at the Faculty of Biology

University of Mainz

Germany

Johan Auwerx

Professor and Nestle Chair in Energy Metabolism

Ecole Polytechnique Federale in Lausanne

Switzerland

Yves Barral

Associate Professor of Biochemistry

Department of Biology
ETH Zurich

Switzerland

10. Sponsors

ERIBA

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Ministry of Economic Affairs, Agriculture and Innovation

Ministerie van Economische Zaken

The Province of Groningen

provincie groningen

Collaboration of the Northern Netherlands (SNN)

SNN

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European Union
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The Noaber Foundation

noaber foundation

The Pediatric Oncology Foundation Groningen (SKOG)

SKOG
stichting kinderoncologie groningen

ERIBA

COORDINATION

Megha Upadhyay

SECRETARIAL SUPPORT

Sylvia Hoks
Karin van Wageningen
Joke Eleveld

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