ERIBA

European Research Institute for the Biology of Ageing

To better understand what causes ageing

university of groningen

University Medical Center Groningen

Foreword

A better understanding of the cellular processes that cause ageing is important from a scientific as well as a “healthy ageing” perspective. This is the research area of the European Research Institute for the Biology of Ageing (ERIBA). This brochure explains why such research is important and what it is that we do.

Research on the biology of ageing has been carried out for decades by numerous scientists all over the world. Yet our knowledge of the cellular processes that have been implicated is still far from complete. Fragmentation and compartmentalisation of the very wide research area is partly to blame. However, the insights that do exist also need to be better integrated. As a new institute, ERIBA aims to play a major role in the acquisition of new knowledge as well as in the integration of existing knowledge in all areas related to the biology of ageing.

In 2007 the first plans were made at the University Medical Centre in Groningen (UMCG) for a new research Institute that could support, via fundamental research, the strategic choice for ‘Healthy Ageing’. Collaboration was sought with the University of Groningen and other local, national and European partners. In 2009 this resulted in a concrete business plan. In 2010 the construction plans were drawn up and ERIBA was born in 2013. We started life in a modern building fully equipped to suit our vision that multidisciplinary work is a key ingredient to achieve breakthroughs in bio medical research.

With lead scientists coming to ERIBA from all over the world, our aim for the next few years is to generate new insights into the biology of ageing right here in Groningen. Knowledge that should benefit people throughout the world!

Peter Lansdorp
Scientific director, ERIBA

Our research: the ageing process at cell level

What happens in our bodies as we age? Why do later in life problems occur in cells that have to constantly divide in order to be able to maintain cell production in, for example, blood and skin? And why does the functioning of cells that do not divide continue to decrease as time goes by? ERIBA is searching for the answers to these questions.

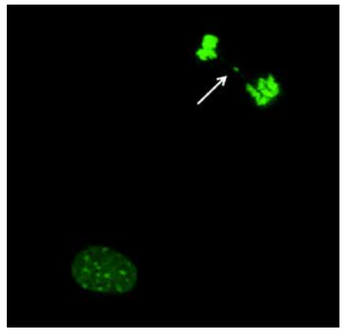
Every day dozens of researchers from The Netherlands and abroad carry out fundamental research into the ageing process and the diseases that go hand in hand with this. Our goal is collect and share knowledge, develop new research techniques and thus make an important contribution to healthy ageing.

ERIBA stands for European Research Institute for the Biology of Ageing and was founded in 2013. We are located in the city of Groningen and we work in a new building that was specially designed and equipped to suit our research approach. ERIBA is part of the University Medical Centre Groningen (UMCG) and the University of Groningen (RuG). Researchers from the two institutes work closely together. Our research groups are led by top international scientists, many of whom have come to Groningen specially to work at ERIBA.

Aspiring scientists will find that ERIBA provides an excellent training platform which prepares them very well for the internationally competitive field of life sciences in the 21st century.

Floris Foijer: chromosomes, ageing and cancer

Around two thirds of all cancers shows chromosome instability: during cell division the chromosomes are not distributed equally between daughter cells. But chromosome instability does not in itself cause cancer. ERIBA group leader Floris Foijer tries to elucidate the link between chromosome instability, ageing and cancer.



‘Cell division is really aesthetic,’ says Floris Foijer, and he produces a video clip to prove his point. ‘Look, here we’ve marked the DNA with green fluorescent dye, and the spindle microtubules in red.’ The vague circumference of a cell is visible in the microscopic images forming a time lapse video. Suddenly the DNA condenses into thick chromosome bodies in bright green and the red mitotic spindle forms. Then the chromosomes are divided. ‘Look, there!’ Floris points to the screen. A small green dot lies lost between both sets of chromosomes. ‘There’s a chromosome that got lost and ended up in the wrong cell. That is how chromosome instability results in aneuploidy.’ Aneuploidy means that cells have the wrong number of chromosomes. A well-known form of aneuploidy is Down Syndrome, where patients have an extra copy of chromosome 21 in all of their cells. ›››

‹‹‹ Trained as a biotechnologist and process engineer at Wageningen University, Floris developed a keen interest in medical research. This led to a PhD project at the Netherlands Cancer Institute NKI in Amsterdam. ‘There I discovered a control mechanism, a sort of emergency brake to stop cell division. But the mechanism came at a price: when these cells started dividing again, they were susceptible to chromosome instability, a failure to maintain the correct number of chromosomes.’

Two thirds of cancer cells show chromosome instability resulting in aneuploidy. ‘Aneuploidy probably predisposes cells to cancer. But not all cells with the wrong number of chromosomes become cancerous. You need something in addition, such as a mutation that shuts down the cancer suppressor gene p53.’ After moving to ERIBA in 2011, Floris continued to work on the role played by chromosome instability in cancer and in ageing. He set out to make a mouse model in which he could study the effects of instability under controlled circumstances. The effort was a success, and led to a unique mouse model. ‘We can now create mice that have chromosome instability in specific tissues.’

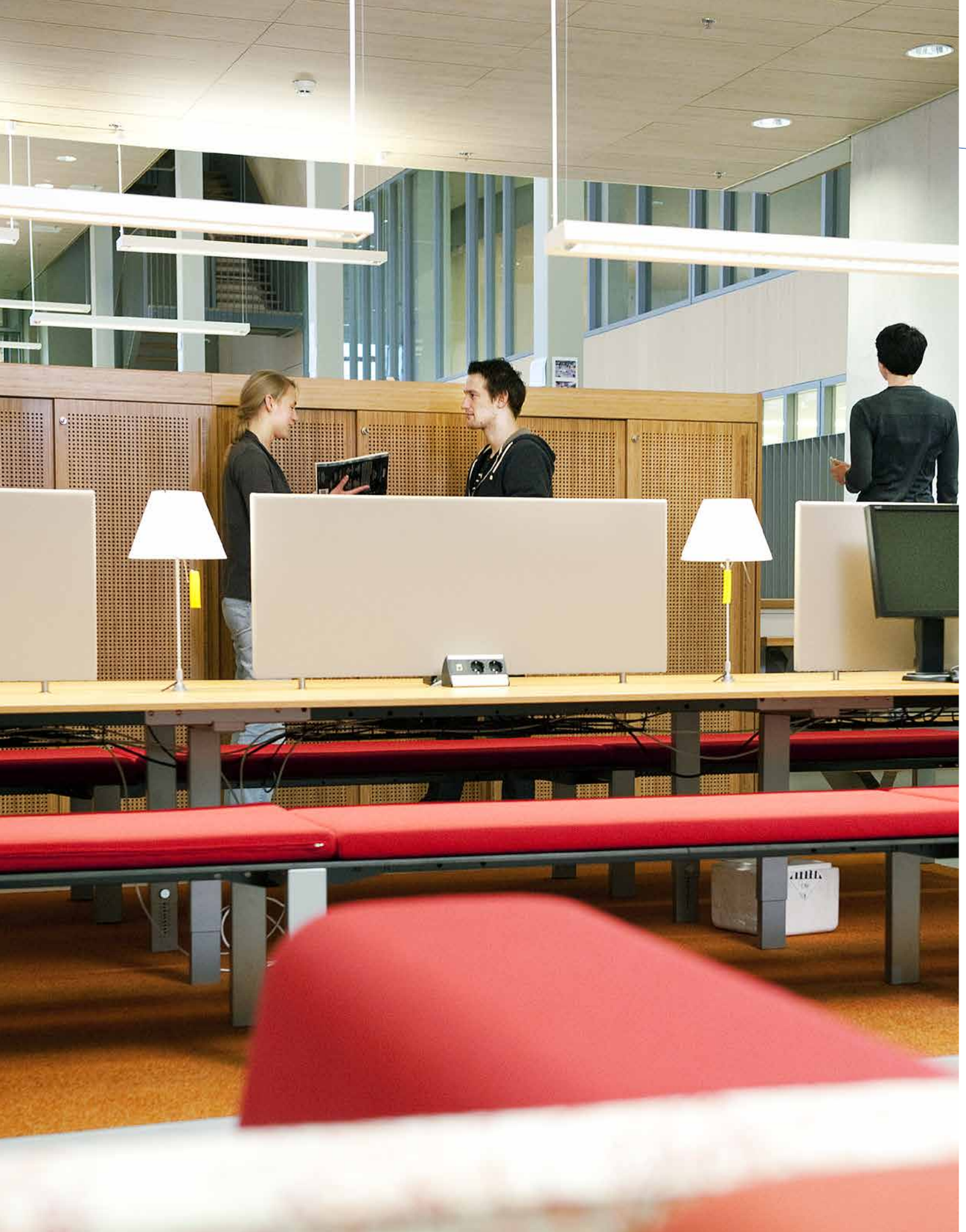
Last year he produced the first results, using mice with chromosome instability in the skin. ‘An interesting observation is that the stem cells in hair follicles died off, while the skin stem cells survived. But the skin showed dramatic aneuploidy.’ Apparently, hair follicle stem cells cannot handle chromosome instability and perish, while the skin cells survive. ‘The interesting question for me is: would it be possible to make cancer cells behave like those hair follicle stem cells, so that the chromosome instability will kill them? But to get there, we need to understand what is happening in different tissues.’

Another finding is that aneuploidy causes cells to use more energy because more genes are active. That would seem logical: if a cell has an extra chromosome, it produces extra copies of many genes on that chromosome. ‘But you would expect the cancer cells to do something about this, such as shutting down those superfluous genes,’ says Floris. ‘But they don’t.’ The extra energy they put into the activity of these extra genes causes metabolic stress: energy production is driven into the red. ‘That makes the cells really queasy. And this stress is a marker of cancerous cells, so it is a possible target for anti-cancer therapies.’

But what does all of this have to do with ageing, the central theme of the ERIBA institute? Floris smiles. ‘A good question. First, the chance of getting cancer increases with age. But more directly, in the aneuploid skin of our mouse model we saw no cancer but we did see increased ageing. A collaborator of ours noticed the same in a different model.’ Possibly, aneuploidy causes rapid ageing, which eventually causes cancer. ‘Control mechanisms that prevent aneuploidy will cost the cell energy. So maybe fast dividing cells have sloppier controls, which would be acceptable for skin cells that last only three days.’

Floris would be interested to know whether there is a greater degree of aneuploidy in the skin of old people. ‘We could answer this using the LifeLines biobank, which stores biological material and health information relating to 165,000 people in the Dutch northern provinces. Perhaps aneuploidy could have a prognostic value for cancer or ageing.’

Having access to LifeLines, which was launched by the University Medical Center Groningen, is one of the advantages of working at ERIBA. ‘But also the fact that I can collaborate with clinicians in, for example, oncology or pathology. And, of course, the collaborations inside ERIBA. I find that all ERIBA Group Leaders have some link with my own research, even though they work on different subjects with different model organisms. That truly stimulates collaboration.’ And all that is paying off. ‘I’ve obtained some wonderful results. There are a few interesting papers in the pipeline.’



Our mission: healthy ageing

People who live in developed countries are living increasingly longer. Statistics Netherlands (Centraal Bureau voor de Statistiek) has estimated that the number of centenarians in The Netherlands doubled between 2000 and 2014. In 2025 this number will have doubled again. But a long life is not a goal in itself for most people. We want to age healthy so that we can lead an active life until we reach a very old age.

The socio economic impact of an ageing population is manifold. Yet, we know little about the processes that cause ageing and their role in the development of age-related diseases such as cancer, Alzheimer's disease and Parkinson's disease. ERIBA scientists are trying to better understand these causes using fundamental research. In addition, they are also developing new research techniques and methods. Our efforts should result in new drugs or treatment methods for the above diseases.

Focus on training of young talent

In addition to its research tasks ERIBA focuses on the education and training of scientific talent. We are constantly on the lookout for excellent PhD students. In ERIBA they can undergo focused training in the field of ageing research. We are also committed to the education of masters students and we play a coordinating role in European Marie Curie Initial Training Networks. Postdoctoral fellows are given the freedom and support to work on their research in an inspiring, professional environment.

Our approach: curiosity, collaboration and communication

Researchers from various disciplines and countries collaborate in ERIBA in multidisciplinary teams. We invest in joint projects with departments from the UMCG and the RuG and with other institutes from The Netherlands and abroad. We look further than the boundaries of our own discipline.

This approach requires good, frequent communication. ERIBA's modern building is fully equipped for this. Researchers share their facilities and workplaces in the laboratory and the large offices are perfectly suited for interaction. Moreover, every floor has comfortable meeting places.

The ground floor of our transparent building contains an exhibition room and is open to interested members of the public. This way, as a knowledge reference centre for the biology of ageing we are literally open to questions and suggestions from society. ERIBA thus gives shape to the three pillars supporting its approach: curiosity, collaboration and communication.

ERIBA investigators address questions about ageing using collaborative, multi-disciplinary and technology-oriented approaches.

Victor Guryev: digging into the Dutch genomes

We all know that subtle alterations in our DNA can cause diseases. But small mutations are not the only changes that affect our genes. Structural changes such as deletions, duplications and similar events might be of greater influence on healthy ageing than ‘classic’ mutations. ERIBA Group Leader Victor Guryev has examined these changes in the Dutch genomes, and has made several highly interesting findings.

In summer 2014, a national consortium led by UMCG geneticist Cisca Wijmenga published an inventory of the Dutch DNA, the Genome of the Netherlands (nlgenome.nl) study, in the journal Nature Genetics. They read the entire DNA sequence from 250 trios (each consisting of two parents and one or two children) to understand genetic diversity in the Dutch population, but also to study DNA differences that might cause diseases. One of the study authors is bioinformatician Victor Guryev, Group Leader of the Laboratory of Genome Structure and Ageing at ERIBA.

Bioinformatics combines biological insight with computer science, statistics, mathematics to study and process the huge amount of genetic data that scientists produce these days. The Genome of the Netherlands study (GoNL), for example, produced about 50 terabytes of data and its interpretation required a consolidated effort of several national and international groups. ›››

‹‹‹ ‘I was trained as an experimental biologist, at Novosibirsk State University, and got interested in bioinformatics when I was trying to understand the data that was generated in my master project,’ Victor explains. At the Dutch Hubrecht Institute for Developmental Biology and Stem Cell Research he developed analytical tools to study genomes, first in model organisms such as the worm C. elegans and laboratory rats, then in humans. That is how he became part of GoNL.

Victor’s focus is on the detection of structural changes and the prediction of their functional role. These are differences that can span from a few to thousands of base pairs, the letters in which the genetic code is written. Letters can be lost (deletions), moved (translocations) or inserted (insertions). ‘We know a lot about the effect of point mutations, where just one letter in the genetic code is altered,’ he explains, ‘but it is clear that structural changes in our genomes are at least as important as single nucleotide substitutions.’

Victor discovered that one in seven children in the GoNL families had new structural change(s), these were not present in their parents’ DNA. ‘And what is truly striking, structural changes hit ninety times more bases and sixty-five times more gene coding sequence than do point mutations.’ So, even though new structural changes are much rarer than point mutations, Victor reasons they may very well be more important to study in relation to human diseases, as they have a greater impact.

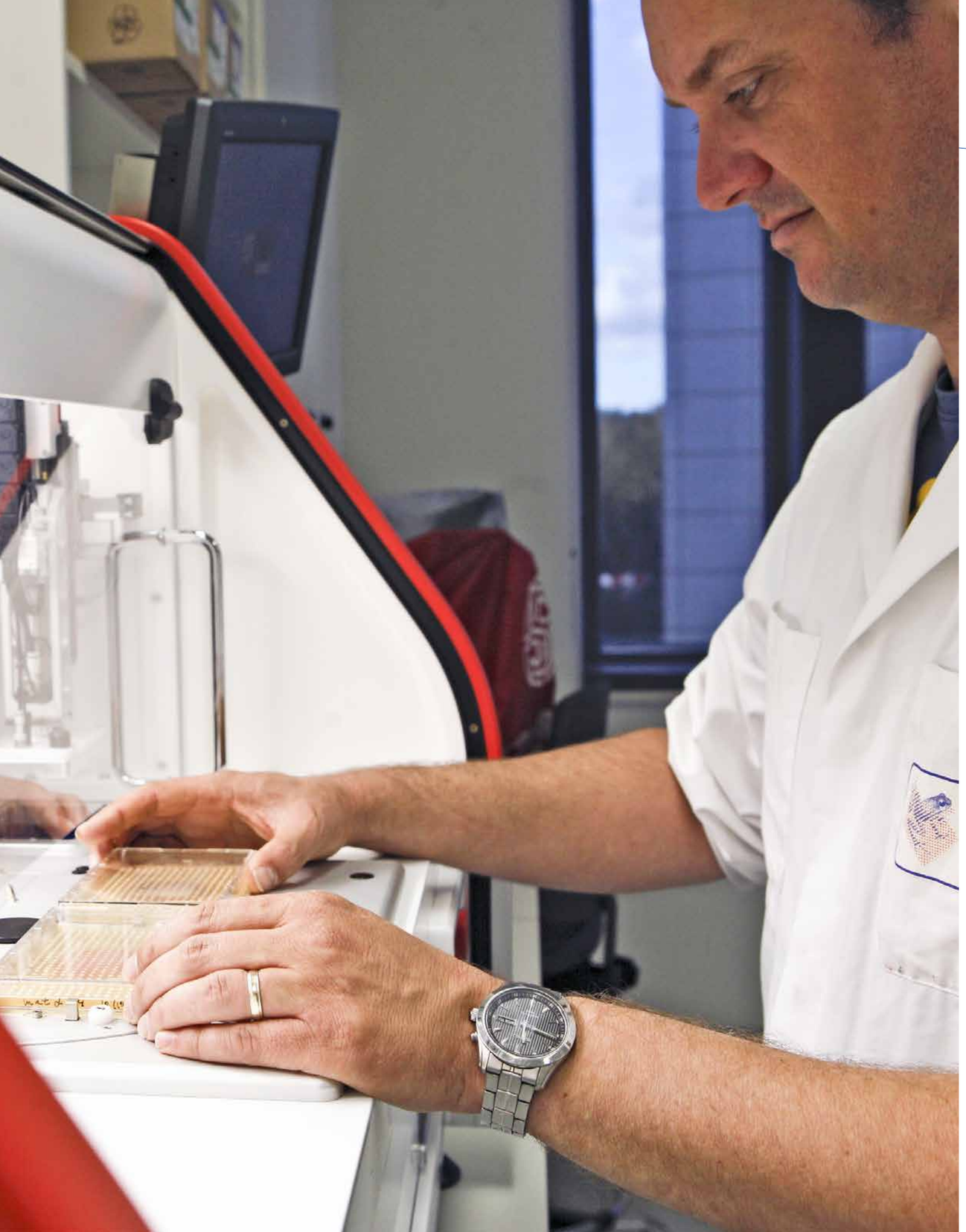
But that is not as easy as it sounds. Until now it has been technically very challenging to detect small structural changes that affect between 20 and 1,000 letters of the DNA code. ‘But in our Genome of the Netherlands study we’ve made huge progress in detecting and validating these small changes. We combined several bioinformatics approaches that allowed us to see structural mutations of any size. That was a real breakthrough!’

When he first got involved in the GoNL project, Victor was head of bioinformatics at the Hubrecht Institute. In the summer of 2012 he moved to ERIBA. ‘For me it was the logical next step. I had moved from different model organisms to humans. And ageing presents several questions on which structural changes in the genome have a bearing.’

As we age, the genomes of our cells inevitably experience DNA damage and carry out repairs. However, this process is not 100% error-proof and gives rise to cells that bear mutations in their genomes. When these cells divide, their daughters will carry the genetic defect. ‘It is difficult to investigate, as it results in mosaicism, where some cells have defects, but other don’t.’ However, finding cells that have acquired a genetic defect in the otherwise normal tissues of ageing people is a major challenge.

It is these types of questions that Victor is now investigating at ERIBA. ‘How do genomes change during ageing, what are the players?’ Mutations that accumulate during our lifetime contribute to many of the processes and diseases associated with ageing. ‘The fewer mutations you get, the longer you might live. So it would be great to find a way to reduce the mutational load.’

At ERIBA Victor has access to the LifeLines biobank, which collects genetic and environmental data relating to 167 thousand people in the northern provinces of The Netherlands. This allows him to study the effects of mutations that occur during a lifetime. ‘One of the most interesting findings from Dutch genome data is that there’s a difference in susceptibility to new structural changes in the DNA among the human population.’ While Victor’s focus is now on human studies, colleagues at ERIBA work with a range of model organisms such as mice, worms or yeast. ‘As the DNA is the same anywhere, most of the effects we find in human population can be studied in detail by experiments using these models.’



Our partners: UMCG and RuG

ERIBA was founded in 2013 as the result of a collaboration between the University of Groningen and the University Medical Centre of Groningen.

We use each other's expertise and facilities. Both institutions have Healthy Ageing as their strategic focus. Collaboration in this discipline has generated other organisations and networks, such as the bio database LifeLines, the Healthy Ageing Network Northern Netherlands and the Healthy Ageing Campus.

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