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CORDIS Results Pack on frontier research for gene editing

Advancing the development of innovative genetic technologies

A thematic collection of innovative EU-funded research results

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Editorial

Advancing the development of innovative genetic technologies

DNA carries the genetic instructions that dictate how organisms develop and function – acting as a blueprint for life. By digging deeper into genetic differences and harnessing the power of gene editing, EU-funded researchers are opening up new possibilities in the medical and biotech fields. This CORDIS Results Pack showcases the scientific advancements made by eight EU-funded projects which are providing fascinating insights into human history, biology and technology.

Gene editing, also known as genome editing, is a technology that allows scientists to make specific, targeted changes to an organism's DNA. This involves adding, removing or altering genetic material at specific locations within the genome. In the field of medicine, genetic therapies have the potential to be used to prevent, treat or even cure certain inherited disorders. Researchers are also looking into how they could be used to treat cancers and infections.

Beyond that, the more we learn about DNA, the more we get a glimpse of how living things function. Studies into DNA have shown us how cells grow, divide and repair, and how critical processes in the body, such as metabolism and immunity, are controlled at the genetic level.

Looking into the distant past, DNA studies can also reveal a great deal about migratory patterns and ancestry. And looking to the future, gene editing potentially opens the door to the engineering of synthetic organisms designed to perform specific tasks. Robots consisting of living cells could be made to be self-powering and self-healing, performing functions that would otherwise be hard to engineer from inert material.

Addressing key medical and societal issues

This Pack presents a diverse portfolio of projects supported by the European Research Council (ERC), which demonstrate how gene editing is helping us to address key medical and societal issues. The ERC is dedicated to funding frontier research that make use of gene editing technologies.

One of these, CRISPR/Cas, has opened new possibilities in both basic science and applied research, enabling researchers to tackle previously unanswerable questions. Over 30 ERC-funded CRISPR/Cas projects have resulted in patents, with some leading to the creation of spin-off companies.

The ERC-funded projects highlighted in this Pack bring together researchers from a range of disciplines including molecular biology, genetics, chemistry and bioinformatics, to name but a few. Together they demonstrate how a focus on basic research can deepen our understanding of biological mechanisms and human diseases, while opening up practical applications in agriculture, biotechnology and medicine.

The knowledge generated through this cutting-edge work will also help policymakers and stakeholders to better understand the benefits and potential risks associated with gene editing, and to take supportive action accordingly.

Cracking the code of DNA folding machines

New research has helped to explain how DNA is shaped into loops, a process critical for ensuring chromosomes are properly distributed during cell division.

When a cell divides, it must duplicate and organise its DNA, an enormous task given the length and complexity of the genetic material. You can think of DNA as a long thread that must be tightly and precisely packed into a tiny space without tangling.

Folding and organising DNA

The CHROCODYLE project, carried out with support from the European Research Council, set out to understand exactly how this packing is achieved. To do this, project coordinator Stephan Gruber and his team at the University of Lausanne in Switzerland focused on structural maintenance of chromosomes (SMC) complexes, protein machines that actively fold and organise DNA. These complexes are essential for keeping genetic material intact, which is vital for cell survival and function.

Our work may help reveal the molecular defects causing these diseases and provide insights into potential therapies.

A key player here is condensin, one of the SMC complexes that shape DNA into loops. These loops are crucial for DNA repair, and for ensuring chromosomes are properly distributed during cell division.

However, the precise mechanics of how SMC complexes move along DNA and form loops has remained unclear. CHROCODYLE aimed to change that.

High-throughput genetic engineering

To tackle this challenge, the team turned to a simpler model organism: the bacterium Bacillus subtilis, which contains a version of the condensin complex that is easier to study than its human counterpart. This allowed the researchers to perform high-throughput genetic engineering, generating over 1 000 mutant bacterial strains with specific alterations in the SMC proteins.

These mutants were then used in a technique called chemical cross-linking to map the molecular structure of the SMC complex with high precision.

“We were able to build a very detailed picture of what the bacterial SMC machine looks like and how its different parts are arranged,” says Gruber.

At the same time, the researchers studied how SMC complexes interact with DNA both in vitro and in living bacterial cells. They used advanced tools such as crystallography, microscopy, ChIP-Seq and Hi-C to observe where and how SMC binds and acts on chromosomes. This combination of structural and functional studies gave them a full view of how the SMC machinery works.

One of the most significant outcomes of this research was the development of a new model for DNA loop extrusion, i.e., how SMCs move along DNA. “The SMC motor moves in large steps and can easily bypass both small and large obstacles on DNA,” Gruber explains. “This is unlike anything previously proposed for other DNA motors.”

From bacteria to breakthroughs

The impact of CHROCODYLE extends beyond bacterial biology. In humans, malfunctioning SMC proteins are linked to congenital disorders and frequently mutated in cancer. The knowledge gained from this project could help us understand the specific molecular errors that cause these diseases, potentially leading to ideas for future treatments.

“Our work may eventually help reveal the molecular defects causing these diseases and provide insights into potential therapies,” adds Gruber.

Additionally, understanding the SMC machine in bacteria could potentially contribute to the development of new drugs to fight bacterial infections. These insights offer a way to address antibiotic resistance, one of the most pressing challenges in global health today.

Finally, the project has also laid the groundwork for future breakthroughs. With new techniques such as cryo-electron microscopy, researchers are now resolving SMC-DNA structures at near-atomic resolution, confirming and building on CHROCODYLE’s findings. This progress represents a significant step forward in the study of life’s essential molecular machines.

PROJECT
CHROCODYLE – Chromosomal Condensin Dynamics: From Local Loading to Global Architecture

COORDINATED BY
University of Lausanne in Switzerland

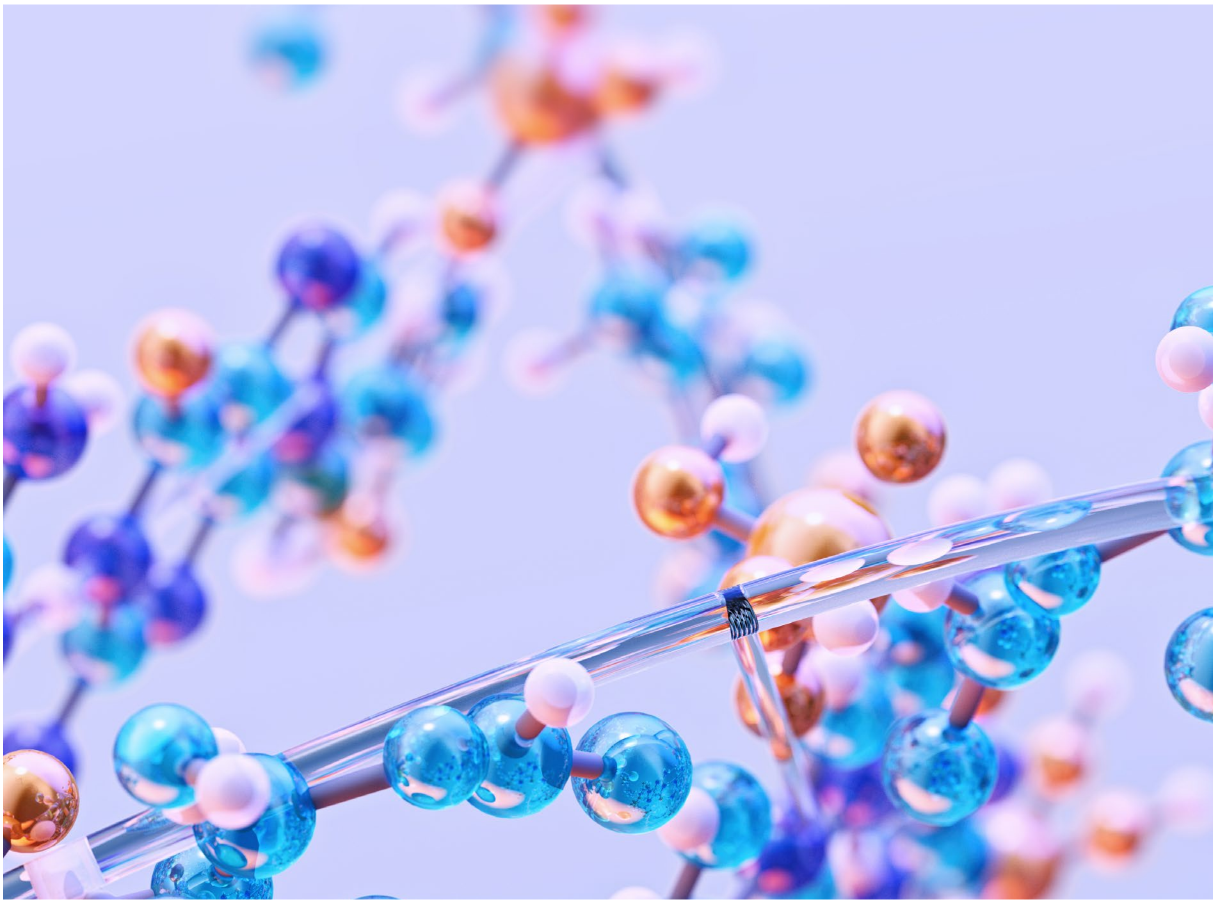
FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/724482

PROJECT WEBSITE
wp.unil.ch/gruberlab

Revealing cellular conflict role in disease and development

Understanding the conflicts that happen within our cells could shed new light not only on disease progression, but also on how our bodies successfully respond.



Conflicts are a normal part of life. Avoiding and resolving them is an important skill that we acquire early on and continue practising on an everyday basis.

"Conflicts however are not only a social phenomenon among human individuals," says ConflictResolution project coordinator Stephan Hamperl from Helmholtz Munich in Germany. "They can also arise inside our body, within our cells."

Investigating transcription-replication conflicts

'Molecular machines' assemble on our chromosomes at distinct locations to perform their dedicated functions. The ConflictResolution project, which was funded by the European Research Council, was launched to investigate how two of these machines, namely transcription to read out gene information and DNA replication to duplicate the genome, are regulated and coordinated.

"Research suggests that there are mechanisms in place to physically separate these two essential processes and avoid what are called transcription-replication conflicts (TRCs)," adds Hamperl. "Nevertheless, this separation is not absolute, and certain regions of the genome can be considered as hotspots where these two machineries meet frequently."

Just as mismanagement of social conflicts can lead to great harm, the same holds true for cellular conflicts. TRCs are therefore potent sources for instability, potentially contributing to cancers, ageing and neurological diseases.

Expanding the toolbox to study cellular conflicts

To better understand this phenomenon, Hamperl had previously built a reporter system for identifying specific encounters between transcription and replication machineries. In ConflictResolution, he used this technique as a starting point to investigate in more detail the impact of these collisions on DNA integrity, with the aim of identifying the protein factors necessary to resolve and overcome them.

"ConflictResolution has extended our toolbox to study cellular conflicts in a breast cancer genome," explains Hamperl. "Cancer genomes show aberrant transcription and replication profiles that can lead to unscheduled TRCs and contribute to the pathological transformation of cells."

The project established a system to map these collision sites and identify associated genetic changes in a breast cancer cell model. It also assessed in vivo the contribution of TRCs during early embryonic development, to determine their contribution to cell transformation during development and cellular differentiation.

Molecular mechanisms behind transcription and replication

A number of important breakthroughs have been made. "For example, we found a histone post-translational modification named H3K79 methylation that is deposited at TRC sites, which can help to resolve the conflict," says Hamperl.

"We also found a total of 88 new factors that are recruited to TRC sites. Among these, we were able to characterise in more detail a factor called CGG-trinucleotide repeat binding factor 1 (CGGBP1). This is a mitigator of genome-destabilising DNA structures and resulting TRCs."

Hamperl also discovered that pluripotent cells – cells that develop into many different types of cells or tissues – poorly coordinate transcription and replication mechanisms and exhibit high TRC levels. "This is a molecular feature that is lost after cellular differentiation into more specialised cell types," he explains. "This shows that different cell types vary in their ability to cope with TRCs."

Using the analytical tools developed as part of ConflictResolution, we can start to fill in a key gap in our knowledge.

All this has helped to confirm that TRCs are a frequent, internal source of genetic and epigenetic instability, and underlined the importance of TRC resolution for cellular health. The impact of these findings could be far-reaching.

"Using the analytical tools developed as part of ConflictResolution, we can start to fill in a key gap in our knowledge," adds Hamperl. "We can now study the molecular mechanisms that coordinate transcription with replication processes and reveal the pathways through which TRCs impinge on cell function." This could help scientists like Hamperl to better understand disease progression and ultimately lead to new therapeutic approaches.

PROJECT
ConflictResolution – Transcription-replication conflicts in disease and development

COORDINATED BY
Helmholtz Munich in Germany

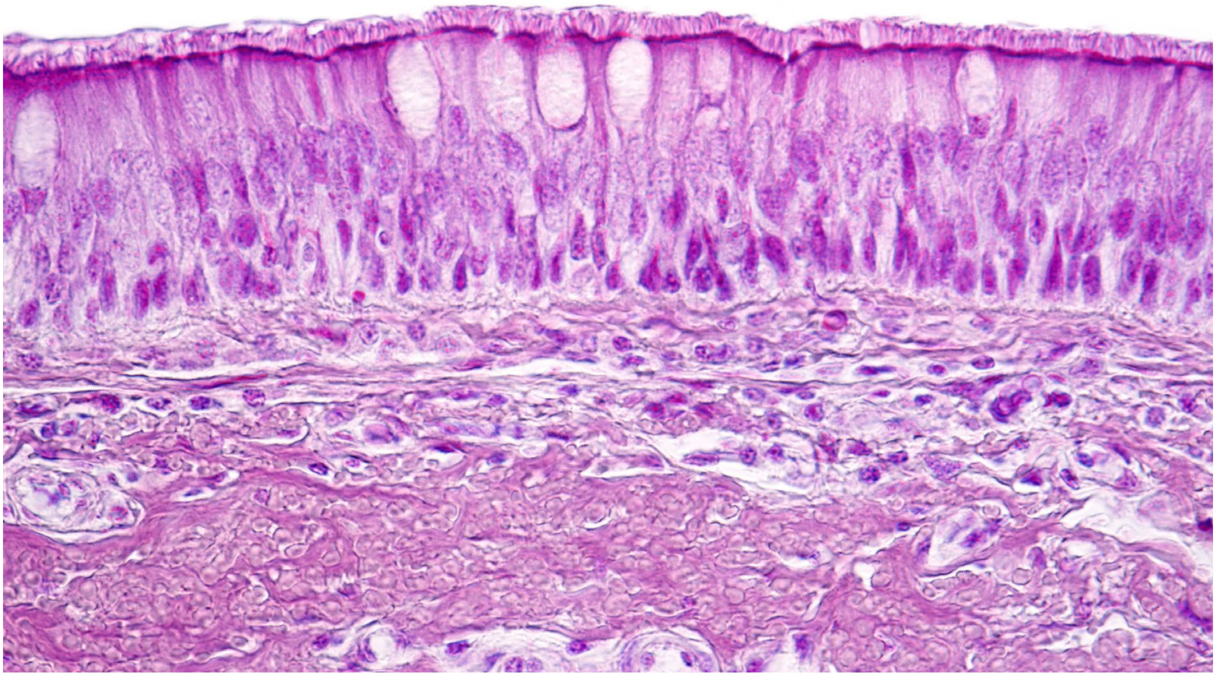
FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/852798

PROJECT WEBSITE
helmholtz-munich.de/en/ies-1/hamperl-lab

Using engineered tissue to energise biohybrid robotics

Understanding the behaviour of epithelial tissue could open the door to both improved health outcomes and next-generation biohybrid robotics.



A thin cellular layer called the epithelia covers every surface of our body, both internally and externally. Examples of epithelial tissue include the outer layer of our skin (the epidermis), the lining of our abdominal cavity, and our sweat glands.

"A good example is the lining of our gut, which needs to absorb nutrients and fluids," says EpiFold project coordinator Xavier Trepat from the Institute for Bioengineering of Catalonia in Spain. "Epithelial tissue acts as a barrier, but on top of that, it is highly specific and highly functional."

This functionality is determined by the three-dimensional (3D) shape of the tissue. How processes such as deformation, growth and remodelling combine to create functional 3D structures however is still largely unknown.

This is something that the EpiFold project, supported by the European Research Council, sought to address. Furthermore, through uncovering the processes that modulate the shape and mechanics of epithelial tissue, the project team also wanted to open the door to the creation of next-generation biohybrid robots. These could one day have applications in fields such as healthcare.

Understanding epithelial tissue behaviour

"We began by developing technology to measure and manipulate the mechanics of these layers," explains Trepat. "We wanted to better understand the behaviour of epithelial tissue, especially in the lining of the gut."

The entire surface of our intestine is renewed every week, thanks to cells that divide and migrate.

To achieve this, organoids – 3D tissue cultures derived from stem cells – were used to study how epithelia adopt 3D shapes. Cutting-edge technologies including micropatterning, microfluidics, optogenetics and mechanical engineering were applied to better understand the behaviour of epithelial tissue.

"We also wanted to see if we could use these dynamic cells to build engineering components," adds Trepat. "Cells have properties that inert materials do not have, such as self-repair and self-powering."

Division, migration and physiological function change

The project was able to pioneer new technologies to measure the behaviour of these cells. "The gut is in a constant state of self-renewal," explains Trepat. "The entire surface of our intestine is renewed every week, thanks to cells that divide and migrate, change their physiological function, and eventually die. It is a very dynamic environment."

The EpiFold project shone new light on exactly how this process works, and how the surface of our gut self-renews. "We now better understand the physical forces involved," remarks Trepat. "We can visualise these processes in vitro, using our organoid combined with our measurement technologies."

Organoid experiments have also shown that metastatic recurrence in colorectal cancer arises from residual EMP1+ cells found in epithelial tissue. This builds on research that suggests that tumours exploit the functions of non-cancer cells in their microenvironment to invade and metastasise.

"The focus of the project was the gut," says Trepat. "However, there are many other tissues – lung, breast and skin for example – where our technologies can be applied."

Turning cells into material building blocks

EpiFold, due for completion in December 2025, will now focus on the most ambitious part of the project – turning cells into building blocks of materials. "We know this will be very hard, but we have already begun to try this," notes Trepat. "We can create small channels made of cells and are looking at generating cellular pumps."

The attraction of using cells is that they are living. Applications could therefore be made to be self-powering and self-healing, performing functions that would otherwise be hard to engineer from inert material. Potential end uses could be in drug delivery and surgery, where deformable materials would be very useful.

"This is high-risk research, and it is still not clear what specific end uses this technology could be for," adds Trepat. This work will take time, as we still have so much to learn about the behaviour of these cellular systems."

PROJECT
EpiFold – Engineering epithelial shape and mechanics: from synthetic morphogenesis to biohybrid devices

COORDINATED BY
Institute for Bioengineering of Catalonia in Spain

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/883739

PROJECT WEBSITE
ibecbarcelona.eu/integrative

Exploring the underlying mechanisms behind brain disorders

New methodological tools help to clarify the genetic variants present in a range of diseases, which could improve clinical practice and future drug development.

Genome-wide association studies (GWASs) screen thousands of genetic variants, comparing the genomes of people with and without specific traits to identify variants associated with disease. These studies have led to deep insights into many diseases, including brain disorders.

Yet despite their potential, GWASs are still limited in identifying the mechanisms underlying brain disorders, in part because the same disorder can arise from various combinations of risk variants in different patients.

In the GWAS2FUNC project, which received support from the European Research Council, a collaboration of researchers aimed to bridge this knowledge and application gap, through the development of new tools to assess the variations present across a range of neurological conditions.

Gene expression signatures at the cellular level

The project was able to develop a method that integrates GWAS results with information on gene expression signatures at the cellular level. Another tool was developed to investigate the potential biological substructure of a disease based on patterns of genomic correlations.

"We have also just recently released FLAMES, a novel tool that improves on predicting what is the most likely causal gene based on GWAS results," says Danielle Posthuma, a statistical geneticist at the Vrije Universiteit Amsterdam in the Netherlands, and the GWAS2FUNC principal researcher. "This helps in defining possible targets for follow-up studies."

The aim is to dive deep into the underlying biology of many brain-related diseases.

Through the GWAS2FUNC project, Posthuma was able to develop these tools based on previous iterations, and to validate them extensively using simulations.

"These tools are able to generate hypotheses with respect to possible underlying biological mechanisms of disease," notes Posthuma. "These hypotheses still need to be validated in functional experiments and ultimately in clinical trials."

Publicly available methodological innovations

These methodological innovations have been made publicly available online. The tools are currently being used by other researchers, as well as by the GWAS2FUNC team through several ongoing projects. For instance, the tools assist in setting up functional experiments to investigate the biological mechanisms of brain disorders, such as Alzheimer's, dementia, schizophrenia and addiction.

The researchers also hope to advance clinical practice in several ways; firstly, by helping to improve predictions of who is at greater risk of developing a certain disease, which can aid in early prevention strategies.

Secondly, the tools will help guide personalised and potentially more effective treatment plans, by predicting how patients that already have disorders will benefit from specific therapeutics. By generating more insight into underlying disease mechanisms, these tools may help in setting up novel treatment strategies or pharma studies.

Developing the tools through large-scale initiatives

The researchers plan to continue improving the tools, using new data that becomes available over the coming years. This includes other large-scale initiatives such as those run at the Allen Brain Institute in Seattle, United States, where researchers are generating large databases of RNA molecules produced in the brain to gain deeper insights into the diversity of cell types.

The GWAS2FUNC team is also working to develop methods to integrate different levels of information from other fields to further improve on interpreting results from GWASs.

Finally, Posthuma is also collaborating closely with scientists to carry out functional experiments that can test the hypotheses generated using the latest GWAS results.

"This is very exciting," she adds. "The aim is to dive deep into the underlying biology of many brain-related diseases."

PROJECT
GWAS2FUNC – From GWAS to functional studies: Tackling the complex nature of brain disorders

COORDINATED BY
Vrije Universiteit Amsterdam in the Netherlands

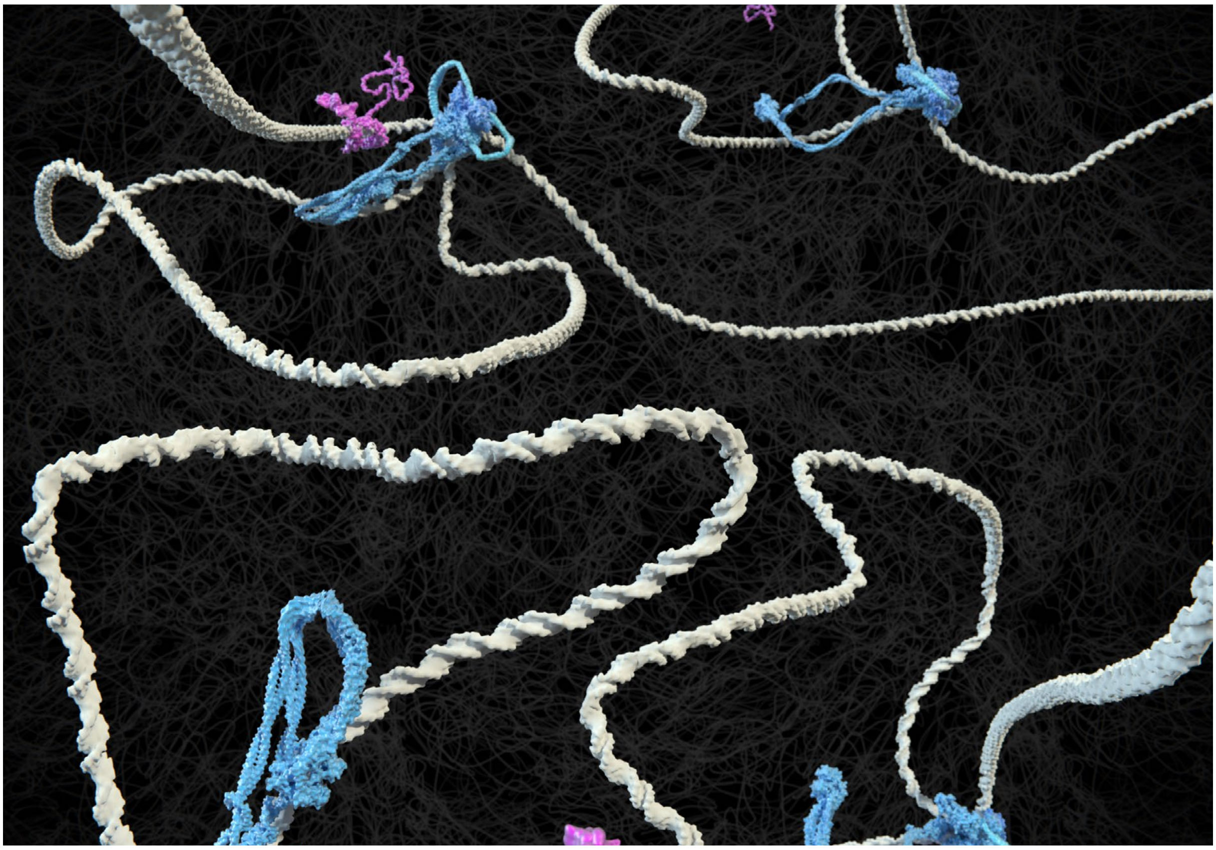
FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/834057

PROJECT WEBSITE
n/a

How molecular motors give chromosomes their structure

As well as being an information processor, the genome is also a physical object, inspiring researchers to explore how its structure determines its function.



Some 150 years ago, Walther Flemming studied chromosomal changes during cell division. Yet despite subsequent advances in knowledge, researchers have only recently identified the key elements that determine the organisation of chromosomes in the nucleus.

"Chromosomes are fundamentally structured in DNA loops, with ring-shaped proteins known as structural maintenance of chromosomes (SMC) complexes, implicated in their creation," says Cees Dekker, physics professor at Delft University of Technology in the Netherlands and principal investigator of LoopingDNA. "The exact mechanisms for how these loops were formed and controlled however, have remained mysterious."

In 2018, Dekker's lab discovered that an SMC called 'condensin' acts as a molecular motor that loops DNA, giving chromosomes their structure.

Now, using single-molecule assays, the LoopingDNA project has revealed more about the mechanisms involved and explored the impact of chromosome structure on biology.

A novel class of DNA motors

Supported by the European Research Council (ERC), the LoopingDNA team used time-lapse single-molecule imaging to follow the condensin-driven DNA looping process in action.

"We put a piece of DNA on a glass slide, visualised it, then saw the loop appearing over time as SMCs attached to the DNA," explains Dekker. "Further experiments enabled us to observe many additional features, such as looping asymmetry and direction changes."

Our 'genome-in-a-box' could one day offer a toolkit for experiments that reveal how chromosomal structure regulates gene expression, offering insights into genetic disorders.

Additionally, the team discovered a new loop motif, called z-loops, formed when two loop-extruding condensin SMCs encounter and pass each other, shedding light on how DNA is organised into a tightly compacted structure.

Loop extrusion was also found to intricately connect to the 'supercoiling' of DNA, which increases the amount of twist in a DNA strand.

"We discovered that SMCs do not merely extrude DNA, but also add a twist with each extrusion, implying DNA supercoiling is regulated by the genome," adds Dekker.

Mechanisms underlying DNA looping

Other fascinating insights have been gained by the project. Cellular DNA is covered in DNA-binding proteins such as nucleosomes or RNA polymerase, that could theoretically impede extrusion. The team were surprised to find this was not the case – SMCs are seemingly capable of subsuming virtually all objects into their DNA loop.

This is significant, as proteins on DNA can be up to tens of nanometres in size, and the ring-shaped SMC is around 30 nanometres across. Dekker found that the ring could even accommodate DNA-bound gold particles 200 nanometres in size, larger than the ring of the extruding SMC itself.

"We concluded that the DNA was not, as previously hypothesised, topologically contained within the SMC complex ring," says Dekker. "We have now worked out a model whereby binding with adenosine triphosphate changes the SMC's shape and size, bringing us closer to understanding the motor mechanism underlying DNA looping."

Insights into genetic disorders

The researchers also set themselves the ambitious task of building a chromosome from scratch. Starting with a length of bare DNA (an *Escherichia coli* bacterial genome stripped of proteins), the aim was to add protein complexes, and other DNA-processing proteins, to study the effects of DNA-organising elements.

While they achieved a basic version, DNA's extreme fragility rendered a fully fledged version beyond the project's resources.

"If we can overcome these technical hurdles, our 'genome-in-a-box' could one day offer a toolkit for experiments that reveal how chromosomal structure regulates gene expression, offering insights into genetic disorders," explains Dekker.

With condensin known to be vital for healthy embryonic development, Dekker's new consortium, currently pursuing funding through an ERC synergy grant, will research this area further. Of particular interest is how DNA looping may enable so-called 'enhancers' to get closer to the promoters of key genes, boosting their expression.

PROJECT
LoopingDNA – Bottom up biophysics approach to resolve the looping structure of chromosomes

COORDINATED BY
Delft University of Technology in the Netherlands

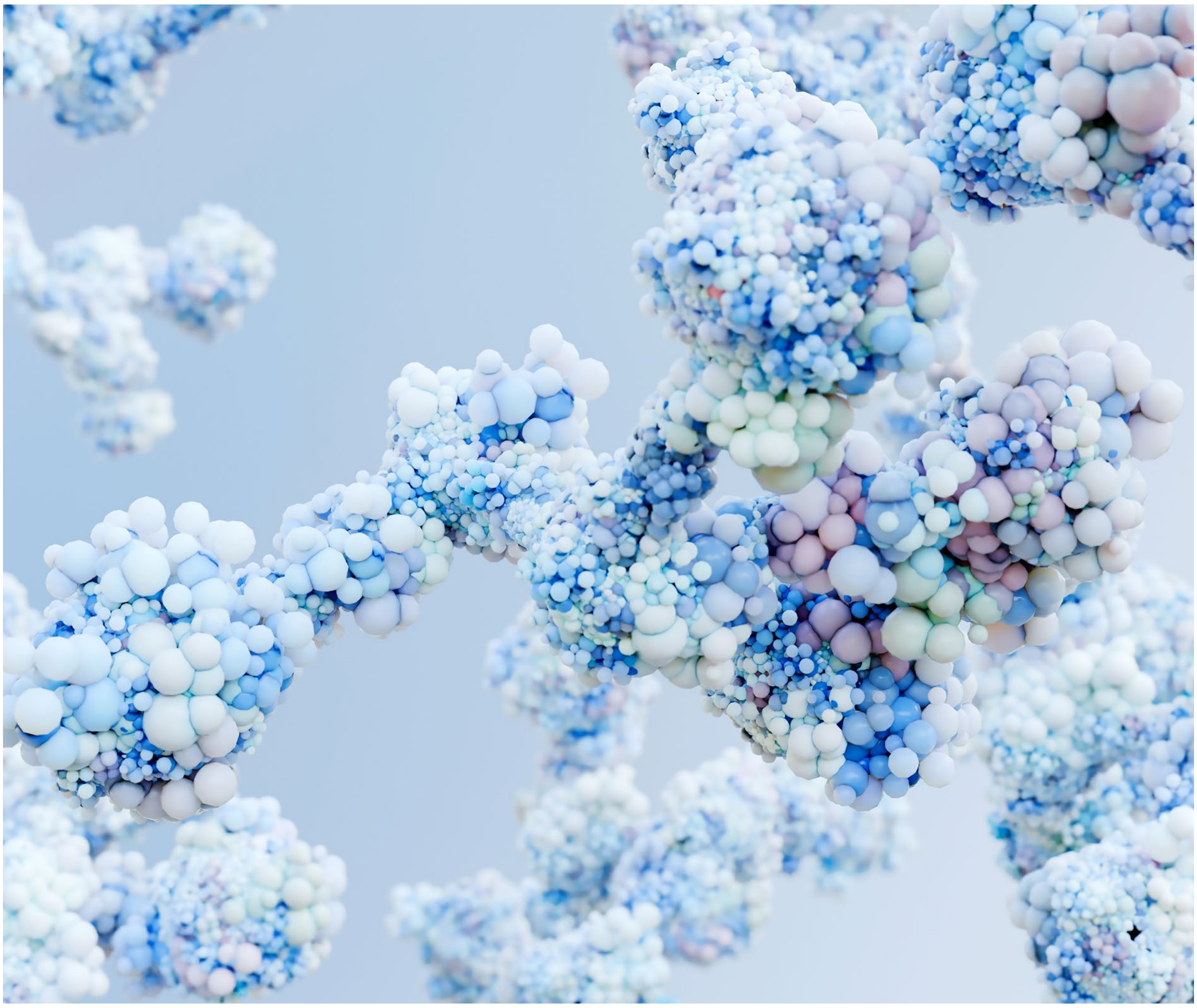
FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/883684

PROJECT WEBSITE
ceesdekkerlab.nl

A new way of designing modular proteins

The design of new proteins that have not yet evolved in nature could potentially open the door to new breakthroughs in medicine, technology and science.



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Proteins are the complex molecules responsible for most of the work done in our cells. They play an essential role in the body's structure, function, regulation and well-being.

But what if proteins could do even more?

"Natural proteins represent only a tiny fraction of all possible protein sequences and structures," says Roman Jerala, a biochemist at Slovenia's National Institute of Chemistry.

The challenge here is to design new proteins that have not yet evolved in nature. "Creating protein structures with new shapes and features could open the door to new breakthroughs in medicine, technology and science," adds Jerala.

Answering this challenge is the MaCChines project, which Jerala led.

The advantages of coiled-coil building modules

The project, which received support from the European Research Council (ERC), aimed to advance the design of modular proteins based on what are known as coiled-coil building modules. Principal investigator Jerala explains that coiled-coils consist of two or more peptide helices (a secondary structure found in proteins) twisted around each other.

Unlike naturally evolved proteins, whose fold is defined by the hydrophobic core, these lab-designed proteins are defined by the arrangement of coiled-coil dimer-forming modules connected into a single polypeptide chain. This chain assembles into a designed pathway that then forms new protein folds.

Natural proteins represent only a tiny fraction of all possible protein sequences and structures.

Dimer-forming modules mediate the interaction of two protein subunits (protein dimers), which are crucial for a range of cellular functions. Scientists can use these modules to design proteins with specific functions and interactions.

"These programmable molecules have many properties and can be produced by cell factories in an energy- and resource-effective and sustainable manner," explains Jerala. "Furthermore, due to their structure defined at the nanoscale, we expect them to be efficient in terms of recognition, delivery and catalysis and to find applications in medicine, biotechnology and other fields."

Results exceed expectations

Using these coiled-coil building modules, the MaCChines project designed and characterised new types of protein cages unknown in nature, regulated their assembly and disassembly using metal ions and proteases, designed their folding pathway, and demonstrated their use for several types of cellular regulation.

"The project has been very productive and, in several ways, even exceeded my own expectations," remarks Jerala.

The project's constructs are available via Addgene and are already being used by other researchers working in the synthetic biology and bio-nanotechnology fields, amongst others.

Modular protein design's role in an AI-based world

Progress moves incredibly fast, and protein design is no exception. In fact, recent AI-based proteins are already fulfilling the dreams of protein designers. However, Jerala is confident that the project's work will continue to have a lasting impact.

"While we are fully embracing generative protein design technology, the principles of modular protein design are something that the AI-based designs cannot do," concludes Jerala. "Some of our designs with experimentally determined structures still cannot be predicted by AI programmes due to their complex topology."

With the support of the new ERC-funded PROFI project and leveraging the foundations established by MaCChines, Jerala's research team is now shifting its focus to the regulation of mammalian cells using designed proteins. They also hope to explore the translation of synthetic biology tools towards therapeutic applications.

PROJECT
MaCChines – Molecular machines based on coiled-coil protein origami

COORDINATED BY
National Institute of Chemistry in Slovenia

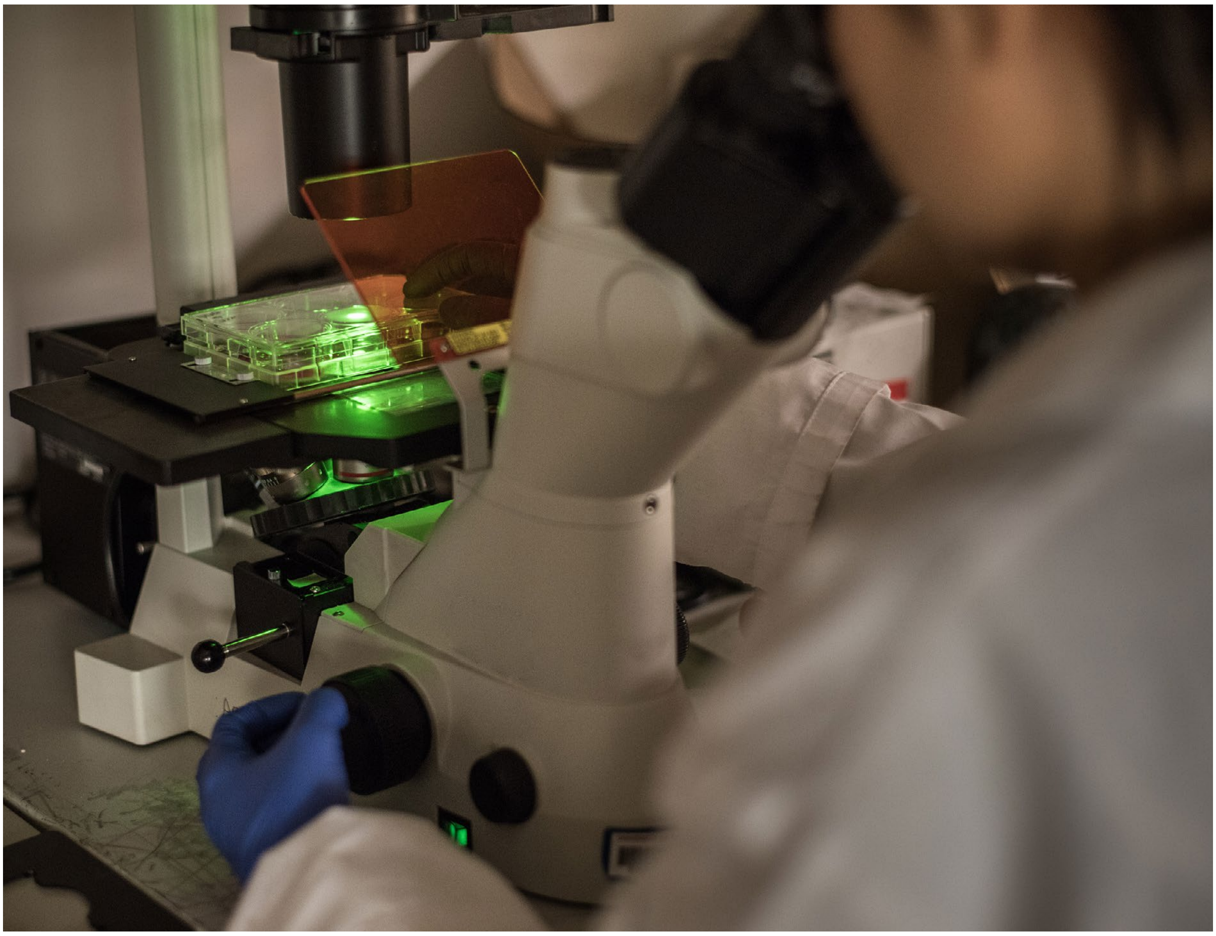
FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/787115

PROJECT WEBSITE
ki.si/en/departments/d12-department-of-synthetic-biology-and-immunology/erc-grants/erc-adg-macchines

Single-molecule biophysics in the high-throughput era

An innovative platform that combines the resolution of single-molecule techniques with the scale of high-throughput approaches could transform biophysics.



The ability to study large libraries of DNA, RNA and protein sequences at the single-molecule level has long been a critical goal in biophysics, one that promises to unlock new dimensions of molecular understanding.

"By allowing researchers to examine the dynamics and interactions of individual molecules, such studies would provide a deeper understanding of biological processes," says Chirlmin Joo, a biophysicist at Delft University of Technology. "It would also open the door to new ways of treating genetic disorders, cancer and other diseases."

Helping overcome this long-standing limitation is the MIGHTY_RNA project, which received support from the European Research Council. At the heart of this initiative is SPARXS, an innovative platform that integrates single-molecule fluorescence measurements with next-generation sequencing to enable high-throughput, sequence-specific biophysical studies.

"This groundbreaking solution allows for the simultaneous kinetic and structural characterisation of millions of molecules with thousands of unique sequences," explains Joo, accelerating understanding of their shape and behaviour.

Overcoming challenges

Developing the SPARXS platform required that researchers overcome several challenges. One of those was ensuring the compatibility of the single-molecule fluorescence detection and the sequencing processes on the same commercial sequencing flow cell.

SPARXS opens up new avenues for understanding sequence-structure-function relationships at an unprecedented scale.

At the outset, researchers were not even sure this would work, as they had no direct control over the conditions inside a sequencing flow cell. "Achieving single-molecule fluorescence [free of background noise] in that environment required rethinking detection strategies from the ground up," notes Joo. "It was a major leap that made SPARXS possible."

Furthermore, to align the vast datasets from the fluorescence microscopy and sequencing modalities, the project had to develop custom algorithms capable of performing precise data coupling.

The datasets, along with all software used in the project, are openly accessible.

One experiment, thousands of unique sequences

Using SPARXS, researchers were able to study the kinetic behaviour of over 4 000 unique DNA sequences in a single experiment. According to Joo, this work not only reveals new insights into sequence-dependent molecular dynamics, but also provides a robust, generalisable framework that can be applied to study proteins, RNA and other biomolecules.

"SPARXS opens up new avenues for understanding sequence-structure-function relationships at an unprecedented scale, and seeing this concept materialise and become experimentally validated has been a turning point of my career," he adds.

How sequence variations influence molecular behaviour

The MIGHTY_RNA project has pushed the boundary of single-molecule biophysics into the high-throughput domain – and it intends to keep pushing. Researchers are currently looking to expand the use of SPARXS beyond nucleic acids, adapting it for studying protein-ligand and protein-peptide interactions.

The project is also exploring the possibility of integrating SPARXS data with machine learning approaches. Such a combination could allow the platform to predict molecular interactions and dynamics, thus enhancing its use in drug discovery and synthetic biology.

"By combining the resolution of single-molecule techniques with the scale of high-throughput approaches, the SPARXS platform empowers researchers to systematically probe how sequence variations influence molecular behaviour, with applications ranging from fundamental biophysics to translational biomedical research," concludes Joo.

He welcomes enquiries from potential collaborators interested in applying SPARXS to other biological systems.

PROJECT
MIGHTY_RNA – Repurposing small RNA from ciliates for genome editing: single-molecule study

COORDINATED BY
Delft University of Technology in the Netherlands

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/819299

PROJECT WEBSITE
chirlmin.org

Calibrating the timing of Neanderthal and modern human contact

Researchers have used tree rings to establish a more accurate timeline for the first meeting between our ancient ancestors and their Neanderthal cousins.

Roughly 40 000 years ago, the fates of our human ancestors and Neanderthals collided. During a window of around 5 000 years, the two species interacted in ways still hotly debated. Thanks to genetic evidence, we know that they interbred, yet pinpointing the exact timing of their interactions has always been tricky.

Radiocarbon results of archaeological materials need to be calibrated against an independent record – a so-called calibration curve. Up until now, this curve hasn't been precise enough to allow us to paint an accurate picture of the past.

"The uncertainties have been so large that, metaphorically speaking, it's like receiving an email today from Julius Caesar," says RESOLUTION project coordinator Sahra Talamo, director of the Radiocarbon Laboratory at the University of Bologna in Italy. "The time signal is that blurred."

Searching for glacial trees

In the RESOLUTION project, supported by the European Research Council, Talamo and her colleagues sought to establish the first accurate chronology all the way back to 50 000 years ago. To do this, they refined the calibration curve using ancient, fossilised trees.

The uncertainties have been so large that, metaphorically speaking, it's like receiving an email today from Julius Caesar.

"This enabled us to significantly advance our understanding of the timing and nature of interactions between anatomically modern humans (AMHs) and Neanderthals, providing key chronological insights that were previously out of reach," adds Talamo.

To establish their chronology, the team first had to identify suitable glacial trees. This quest took them to industrial sand and gravel pits across Italy, and a newly discovered submerged fossil forest just off the coast of Portugal.

Using these trees, the team produced a millennium-long tree-ring chronology for a portion of the last glacial period roughly 18 475 to 17 350 years ago. PhD student Silvia Cercatillo also constructed a 220-year-long tree-ring chronology, which showed ancient trees' value in improving radiocarbon calibration.

A precise chronology of the distant past

The researchers were also able to obtain chronologically precise, directly dated evidence of AMH presence and symbolic behaviour in Europe. This was most notably demonstrated in two significant publications.

In the first, the team reported the discovery of an ivory pendant and an awl (a pointed tool) from a cave in Poland dating to approximately 41 500 calibrated years before the present. In more recent work, the researchers pioneered 'Radiocarbon 3.0.', a more refined dating system that has opened the door to a new generation of radiocarbon science.

"With the precision and methodological innovations achieved in this project, we have laid the groundwork for pushing tree-ring-based calibration significantly further back into the Upper Pleistocene, potentially as far as 50 000 years ago," notes Talamo. "This is not just a scientific milestone, but a transformative step forward for both archaeology and climate research."

A history of hominid co-existence

The RESOLUTION project showed that rather than a broad co-existence between Neanderthals and AMHs, the two likely occupied different regions during specific environmental windows. Their interactions were probably shaped as much by climatic shifts as by cultural or biological factors.

"Thanks to Radiocarbon 3.0. we are no longer confined to general assumptions about when Homo sapiens arrived or how they overlapped with Neanderthals," remarks Talamo. "We now have the means to track these processes as they unfolded in real time."

Beyond the scientific publications, Talamo also published a book (website in Italian) that reflects on the journey of the RESOLUTION project. This aims to inspire young researchers to do research at a similar level.

PROJECT
RESOLUTION – Radiocarbon, tree rings, and solar variability provide the accurate time scale for human evolution and geoscience

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