European Research Council
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Mapping ERC Frontier Research

CRISPR/CAS technology: a revolution in gene editing

Foreword

Over the decades, science has advanced at an extraordinary pace, frequently fuelled by the discovery of new technologies. The emergence of the CRISPR/Cas technology has revolutionised biological research by enabling rapid and affordable genome modification, paving the way for innovative solutions for complex scientific challenges.

Since the seminal discovery of this technology in 2012, the pace at which scientists have embraced and utilised CRISPR/Cas technology has been remarkable, and the ERC's project portfolio is no exception.

This factsheet highlights, for the first time, the significance of the CRISPR/Cas technology for ERC-funded research, mostly in the Life Sciences (LS) domain. Through its 'bottom-up' approach and by selecting projects only based on excellence, the ERC has supported over 1000 scientists using or improving CRISPR/Cas, an investment corresponding to 2.66 billion EUR. In 2022 alone, more than half of the ERC-funded projects in the LS domain involve some use or development of CRISPR/Cas.

The factsheet also demonstrates the importance of basic research in driving technological progress and its applications. Notably, more than 1 in 8 ERC-funded projects using CRISPR/Cas technology fall under applied science, tackling new challenges in fields such as biomedicine, agriculture, pharmacology, and microbial technology.

This example vividly demonstrates how curiosity-driven science can swiftly transform into practical and beneficial knowledge for society.

Introduction

The European Research Council (ERC) is the Europe's leading funding body dedicated to funding frontier research, selecting projects based on scientific excellence only, without any predetermined scientific or policy priorities. This report describes how ERC-funded, curiosity-driven research contributes to the advance of knowledge with the use or development of CRISPR/Cas gene editing technology.

The development and application of CRISPR/Cas technology has likely been one of the most important advances in the life sciences of the past 15 years reflected by the Nobel prize in Chemistry being awarded in 2020 to Charpentier and Doudna "for the development of a method for genome editing". The simplicity, speed, and low cost of generating genetically modified organisms using the CRISPR/Cas technology has no competitor in today's genetic research.

The CRISPR/Cas technology offers tremendous potential across various fields, transforming medicine with cures for genetic disorders, advancing the development of improved crops, or redefining traditional approaches in microbial biotechnology. This technology has great significance for current policy reflections[1] on the deployment of new genomic techniques (NGTs) in the EU and as a means to boost the biotechnology and biomanufacturing sectors[2,3].

Alongside this promise, however, there are also ethical, legal, and safety concerns, including the risks of unintended genetic mutations or human germline editing. These concerns are addressed by the Horizon Europe comprehensive ethical and regulatory framework, which applies to all ERC-funded research[4].

This document provides an overview of the ERC-funded research on gene editing, particularly projects that utilise CRISPR/Cas technology or contribute to its improvement and deeper understanding. It is part of the series of Mapping ERC frontier research reports, on a topic of growing significance from both a scientific and regulatory perspective.

Gene editing and the CRISPR/Cas system

Humankind has been selecting genetic traits for millennia by breeding animals and plants, with the aim to either enhance crop yields or improve food quality to support a growing population. The findings made in modern biology have allowed us to refine this process.

Scientific progress is often characterised by major technological breakthroughs. The generation of monoclonal antibodies, the invention of the Polymerase Chain Reaction (PCR) or the use of fluorescent proteins have had an enormous impact on the life sciences. DNA editing techniques have been widely used to modify genes in a specific and controlled manner. For example, the incorporation of additional copies of a gene (transgenics) or the disruption or replacement of a gene through homologous recombination are genome modification methods used before the development of the CRISPR/Cas technology (Jinek et al. 2012). The characterisation of CRISPR sequences in 1993 (Mojica et al. 1993) and the subsequent development of the technology to modify genes (Jinek et al. 2012, Gasiunas et al. 2012), has completely changed the landscape of genetic experimentation in modern biology.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are DNA sequences found in the genomes of bacteria and archaea that together with the Cas protein act as an immune defence against viruses. This system has been extensively studied and adapted into a cutting-edge tool for precise gene editing, simplifying the process by enabling rapid, cost-effective genetic modifications.

In brief, the CRISPR/Cas system has two main components; a custom-made guide RNA molecule (gRNA) that provides the specificity to target the desired gene, and a 'molecular scissors' (Cas protein) that performs pre-determined cuts in the DNA. This allows researchers to modify specific genes and alter their function in cells, animals, or plants, with wide-ranging applications in basic research, agriculture, biotechnology, and human health (Figure 1).

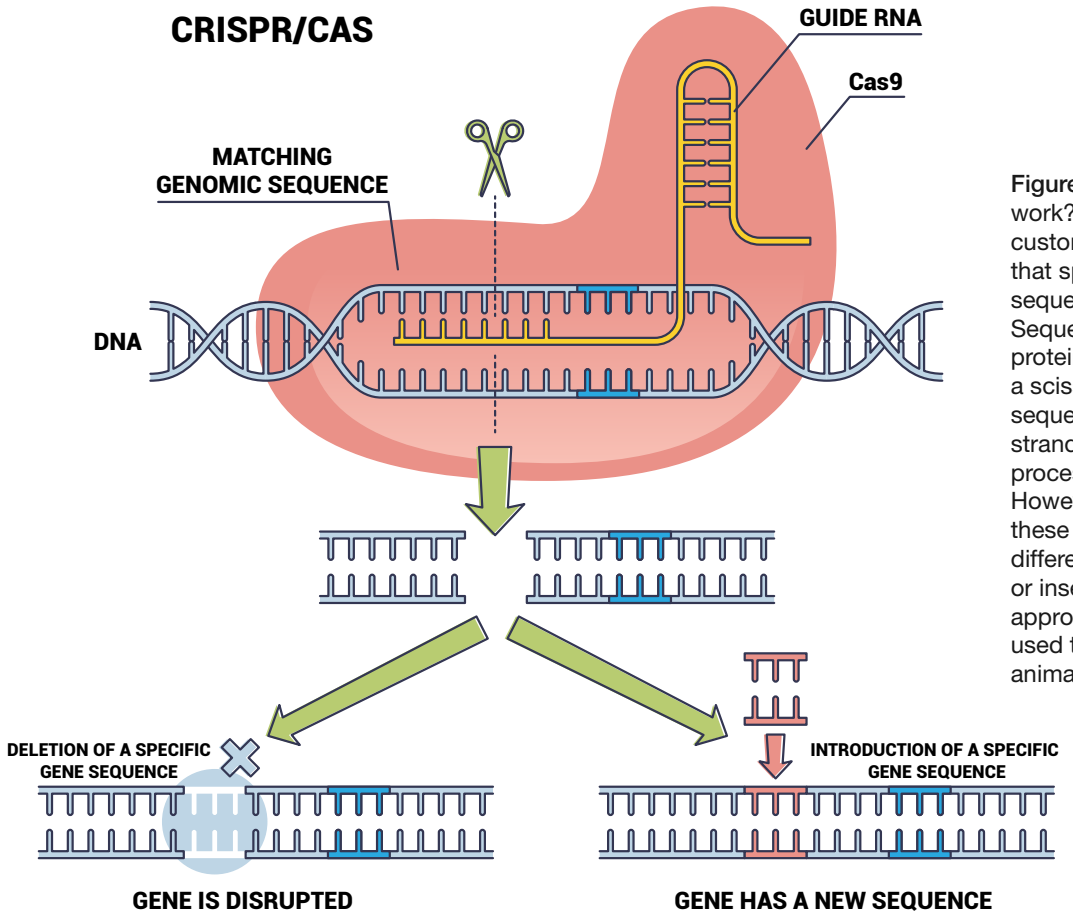


Figure 1: How does CRISPR/Cas work? CRISPR/Cas contains a custom-made guide RNA (gRNA) that specifically recognises a target sequence, or the Matching Genomic Sequence in the figure. The Cas9 protein is an enzyme that acts as a scissor cutting on the targeted sequence. After Cas9 cuts the DNA strands, the cell's natural repair processes kick in to fix the break. However, scientists can engineer these repair mechanisms to achieve different outcomes, like deleting or inserting part of genes. This approach has been successfully used to genetically modify cells, animals, and plants.

ERC Frontier Research on CRISPR/Cas gene editing: Overview

We conducted a comprehensive search based on CRISPR/Cas-related keywords across all Horizon 2020 (2014–2020) and Horizon Europe (2021–2022) ERC-funded projects. We found that 1297 projects, funded with 2.66 billion EUR in total, involved the use or development of CRISPR/Cas technology (Figure 2).

These projects span all ERC Grant schemes and a wide range of scientific fields, but the CRISPR/Cas technology was especially prominent in the Life Sciences (LS) domain, accounting for 1189 projects. In the Physical Sciences and Engineering (PE) domain there were 23 projects, and one in the Social Sciences and Humanities (SH) domain. The remaining 84 projects are Proof of Concept projects (55) or Synergy Grants (29), not included in any of the three domains. CRISPR/Cas projects within the SH and PE domains spanned a wide range of research areas, highlighting the diversity of scientific inquiry this technology enables. These include studies on cognition, nanomaterials, bioengineering, the biochemical and biophysical aspects of CRISPR/Cas, and the development of tools for biomedical applications.

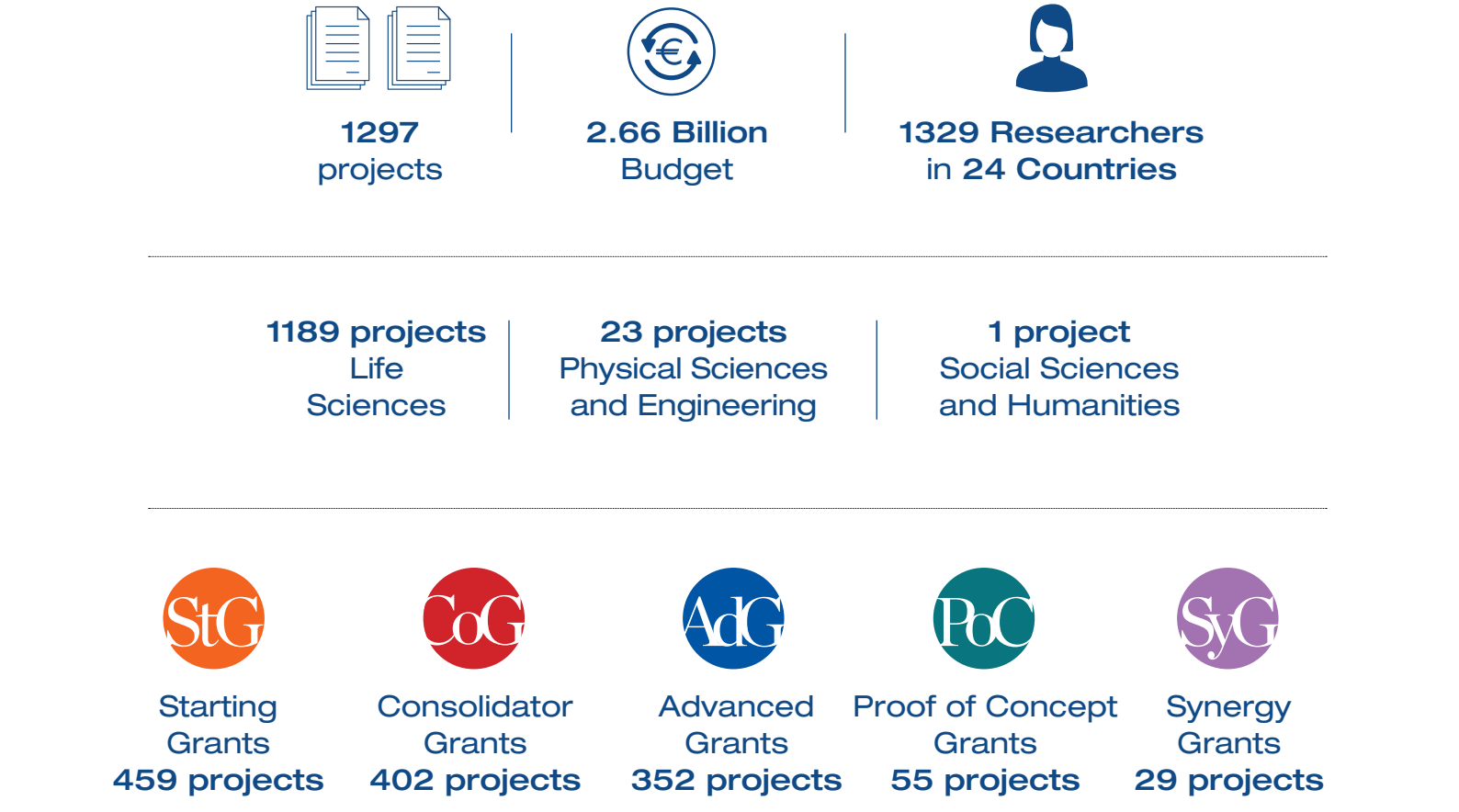


Figure 2: Overview of CRISPR/Cas technology in ERC-funded projects in the 2014-2022 period. StG: Starting Grant; CoG: Consolidator Grant; AdG: Advanced Grant; PoC: Proof of Concept; SyG: Synergy Grant.

As shown in Figure 3, CRISPR/Cas technology was used in 25% of ERC funded life sciences (LS) domain projects as early as 2014, increasing to more than half of the projects in the LS domain by 2022. This growth highlights how ERC funding aligns with researchers' swift and wide adoption of innovative technologies and groundbreaking discoveries.

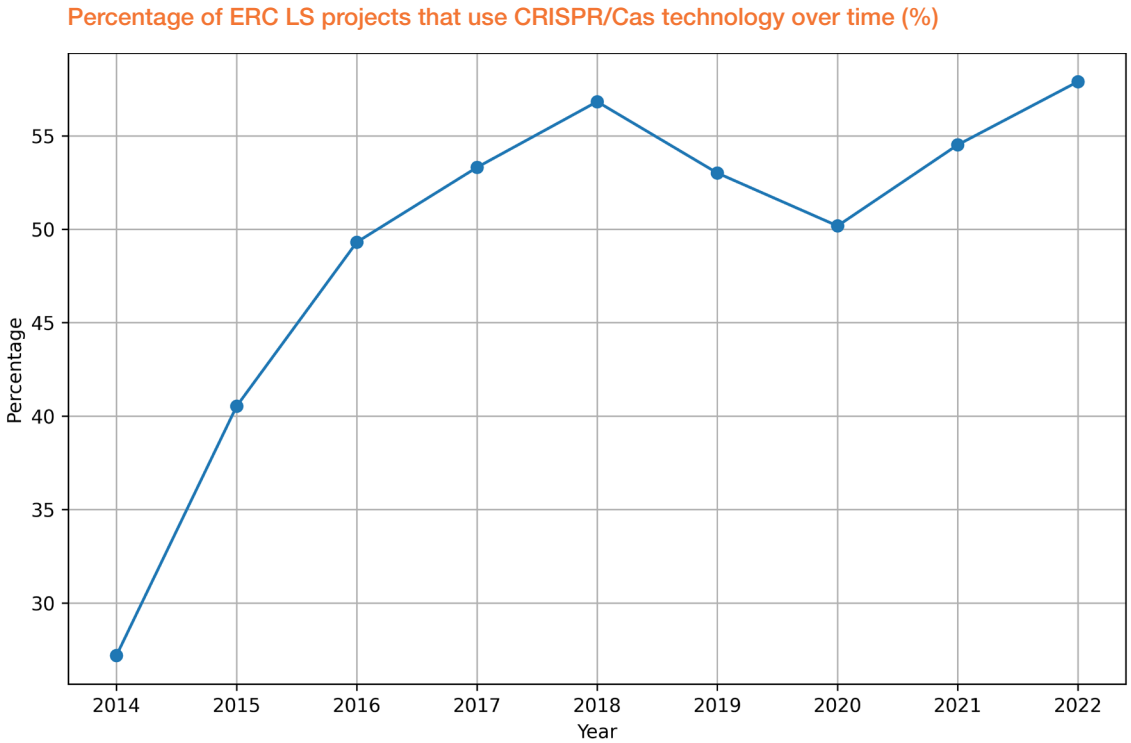
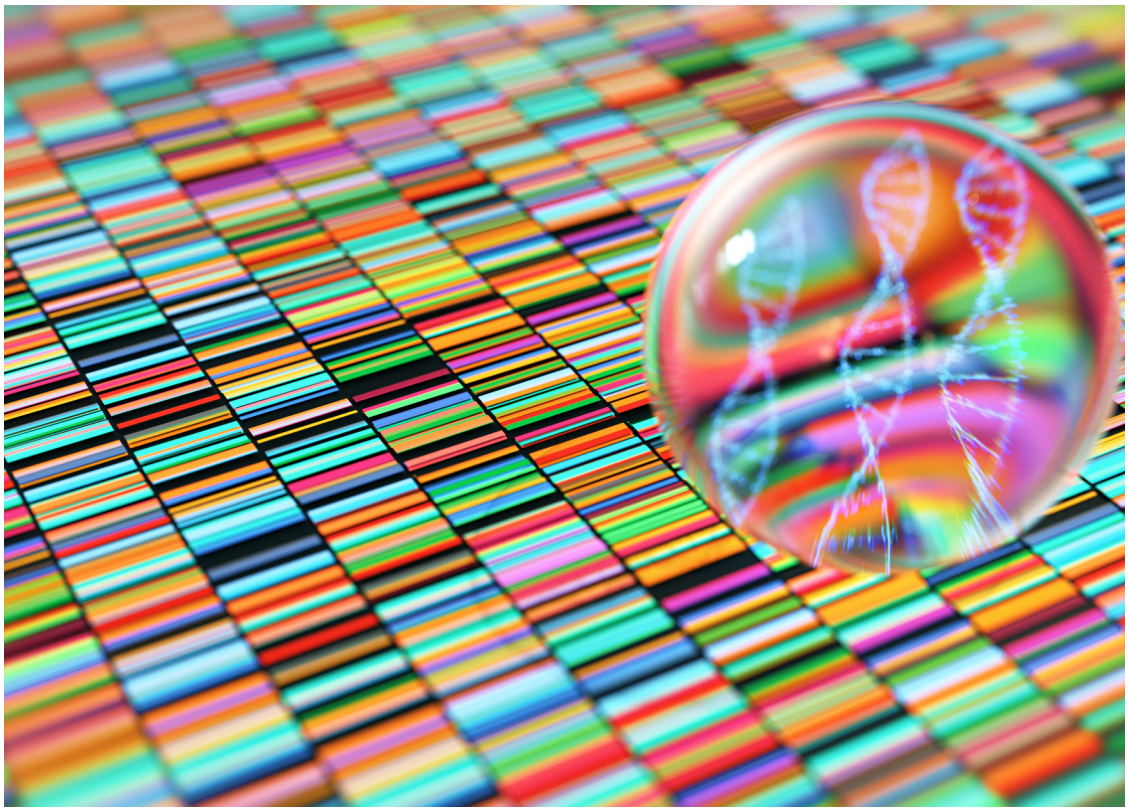


Figure 3: Percentage of ERC Life Sciences (LS) projects that use CRISPR/Cas over time. Since the 2012 original publication by the labs of Doudna and Charpentier (Jinek et al. 2012), the number of ERC-funded projects that use this technology has increased over the years.



CRISPR/Cas gene editing in ERC Frontier Research: from basic science to application

ERC-funded frontier research includes projects that address fundamental questions (basic science), and those that apply existing knowledge to solve practical challenges (applied science).

To distinguish between these two types of projects, the ERC's CRISPR/Cas portfolio was analysed through a systematic classification. The category "basic science" included projects that provide insights into biological principles or mechanisms, including human diseases, or the improvement and study of CRISPR/Cas technology. The second category, "applied science", refers to projects that directly and explicitly address applications, within the following four areas:

- Agriculture and plant biotechnology: generation or study of genetically modified organisms with value for the agricultural industry, such as improvement of plant yield, food quality, sustainability, or disease resistance.
- Microbial biotechnology: microorganisms for industrial applications, including the production of food and beverage, biomanufacturing of chemicals, materials, and biofuels, as well as bioremediation, such as waste management or biodegradation of plastics.
- Pharmacology: drug development, drug discovery, drug screenings including identifying potential drug targets, validating targets through genetic modification, or investigating the mechanisms of action of pharmaceutical compounds.
- Biomedicine: treatment of medical conditions, diagnostics, preclinical or clinical studies to test the safety and efficacy of interventions in human subjects.

Most CRISPR/Cas projects in this study (1,112 projects or 86%) fall into the "basic science" category. The remaining 185 projects or 14% fall into the category of "applied science". Among the latter, the most are biomedical followed by agricultural, pharmacological, and microbial technology (Figure 4).

Percentage of types of Applied science projects in CRISPR/Cas ERC funded projects (2014-2022)

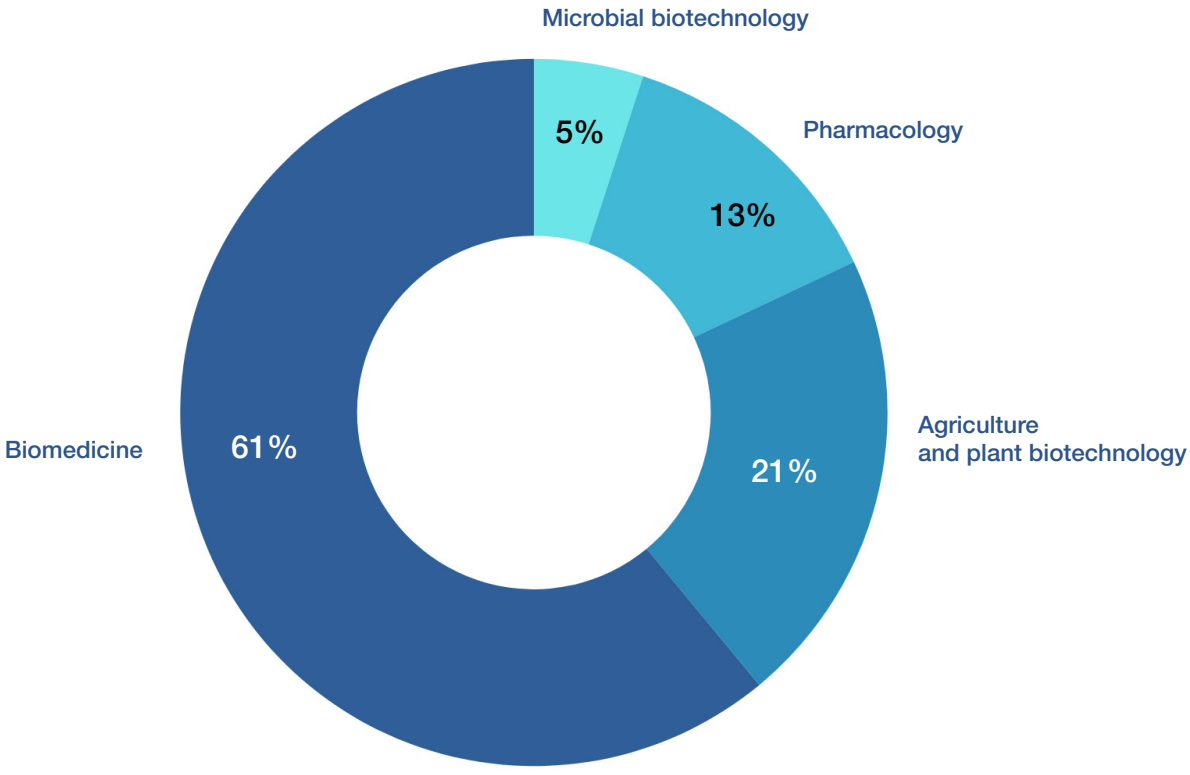


Figure 4: Distribution of ERC-funded CRISPR/Cas projects in the 'applied science' category by area of application.

The portfolio was further analysed using the non-hierarchical Mapping Frontier Research (MFR) taxonomy. This classification system provides an overview of the project portfolio content of the ERC. Figure 5 shows a word cloud representation of both the scientific disciplines (5A) and the main topics (5B) that use or develop CRISPR/Cas technology.

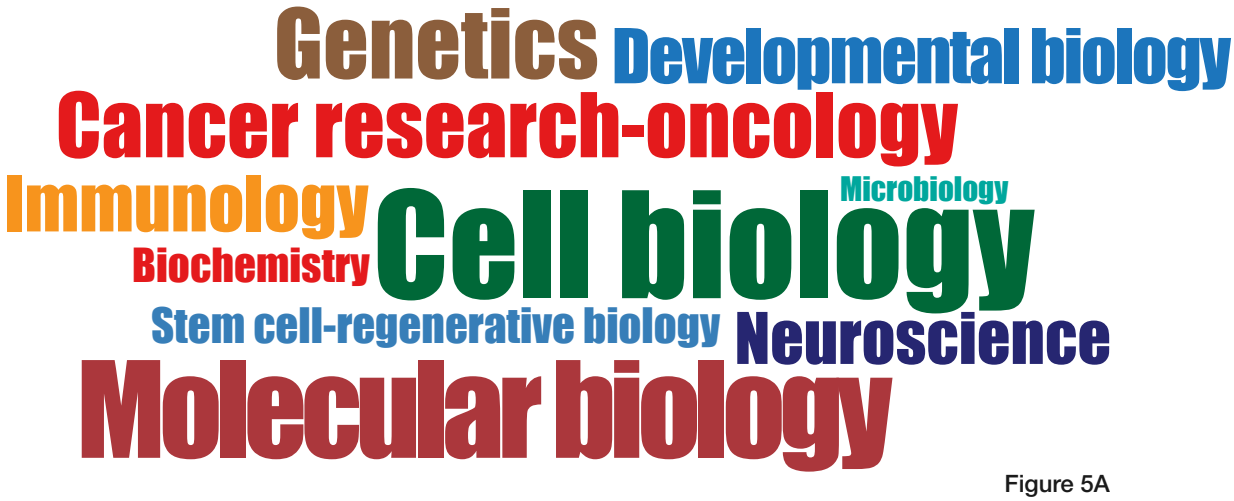


Figure 5A

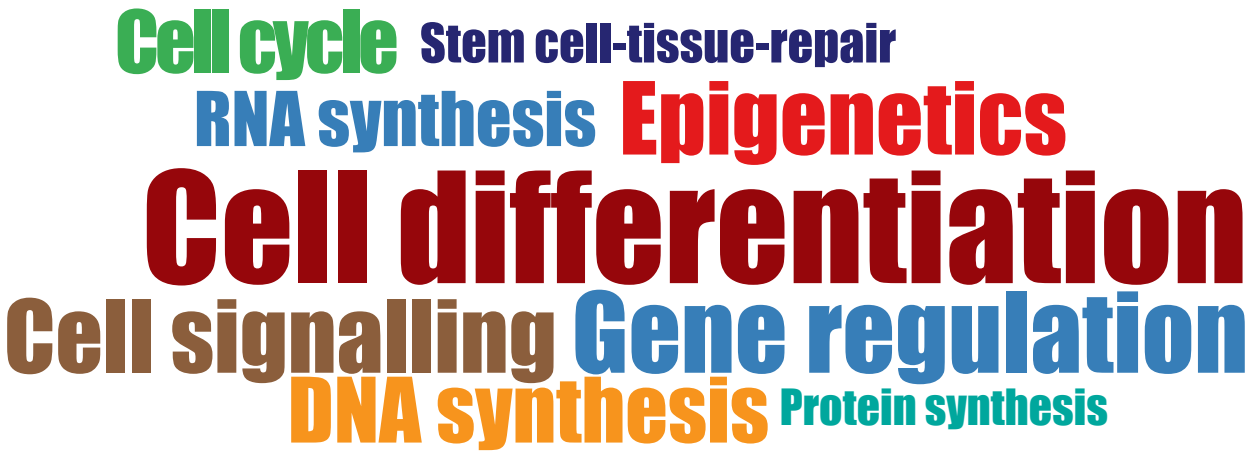


Figure 5B

Figure 5: Mapping Frontier Research disciplines (A) and topics (B) in the CRISPR/Cas portfolio. Both word clouds refer to the projects classified as “basic science”. The word cloud illustrates the frequency of disciplines and topics within the CRISPR/Cas portfolio.

In addition, the CRISPR/Cas project portfolio was examined according to the ERC panel structure[5]. Figure 6 shows this distribution as number of CRISPR/Cas projects per panel, also distinguishing between basic science and applied science projects. The majority of CRISPR/Cas projects in the basic science group were in the LS2, LS3 and LS4 panels, while the projects in the applied science were mainly in the LS7 and LS9 panels.

These data illustrate the wide impact of this technology across various scientific disciplines and the diverse topics addressed within the LS domain. Across the projects analysed, we identified over 30 projects with associated patents, from both the basic and applied science categories, that explicitly mention CRISPR/Cas technology. These include, for example, the development of new RNA sequencing methods or gene therapy for vision impairment.

In the following sections, we give some examples of these projects and the resulting patents and spin-off companies, where available.

Treemap of Panel Distribution CRISPR/Cas porfolio

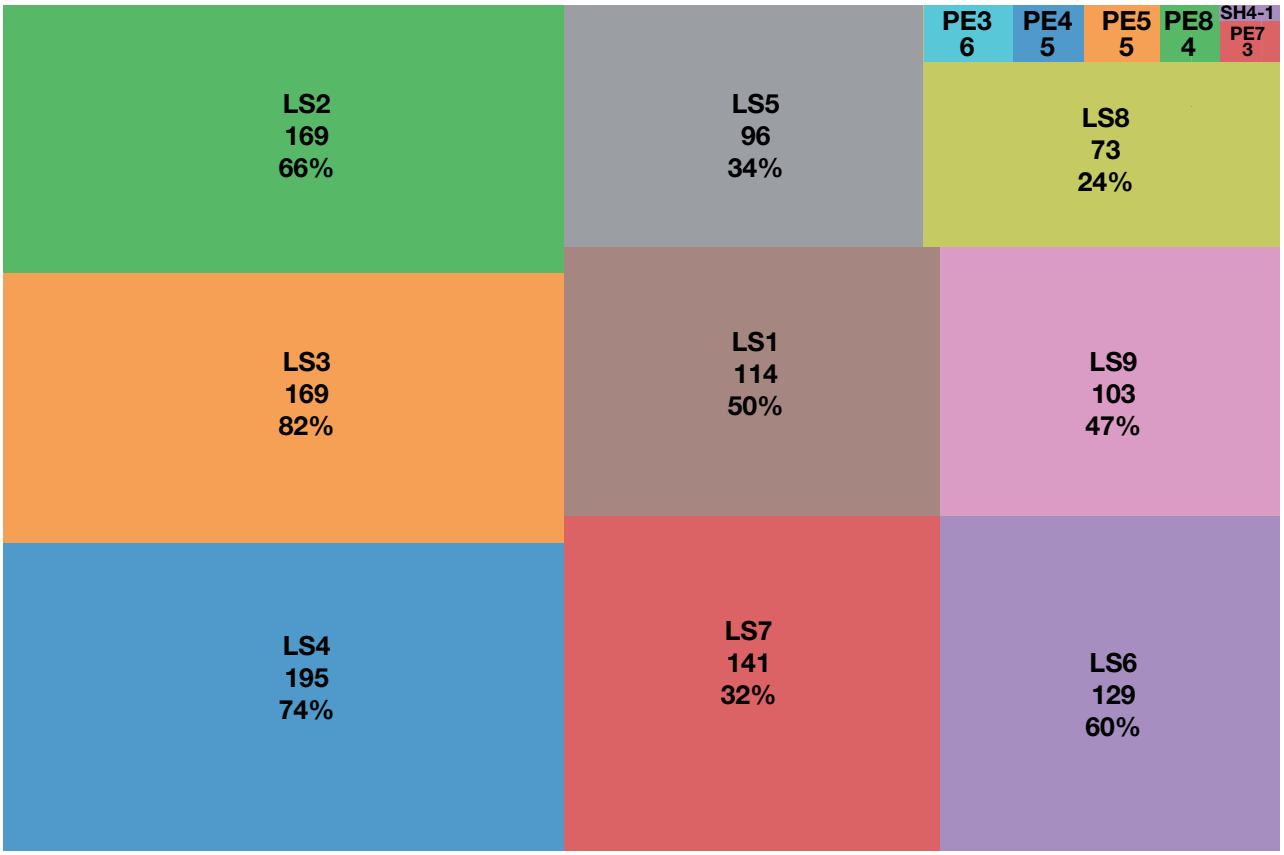


Figure 6A

Figure 6: Treemap of the distribution of CRISPR/Cas projects across ERC Panels for the entire portfolio (6A), for projects classified as basic science (6B), and for those classified as applied science (6C). The figures show the total number of projects per panel. In Figure 6A, the percentage of CRISPR/Cas projects is also shown (when larger than 1%) to illustrate the weight of these types of projects within each panel. The percentage of CRISPR/Cas projects is the average of CRISPR/Cas projects for the last three years of the period considered in this report (2014-2022).

Treemap of Panel Distribution Basic Science CRISPR/Cas porfolio

Figure 6B

Treemap of Panel Distribution Applied Science CRISPR/Cas porfolio

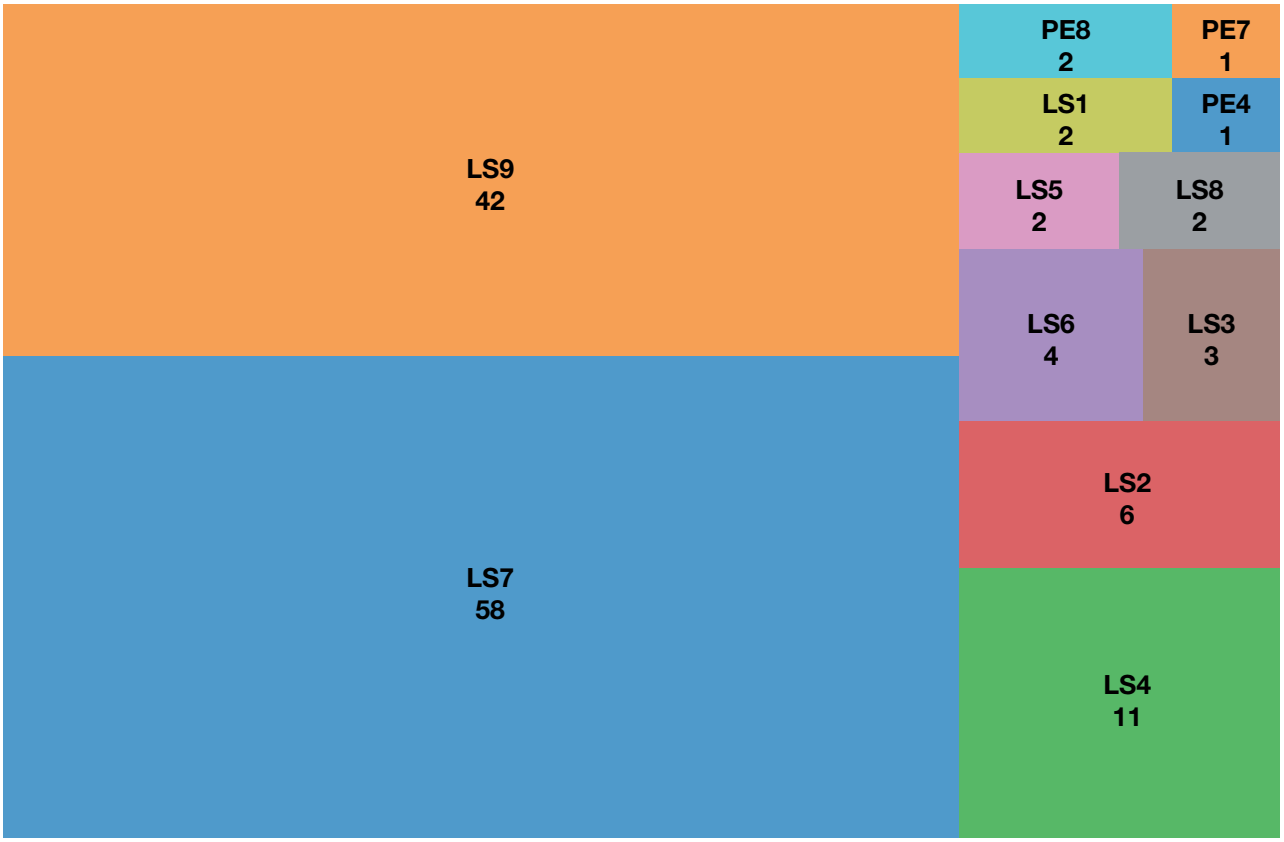


Figure 6C

ERC projects: Examples

The importance and impact of CRISPR/Cas on basic science

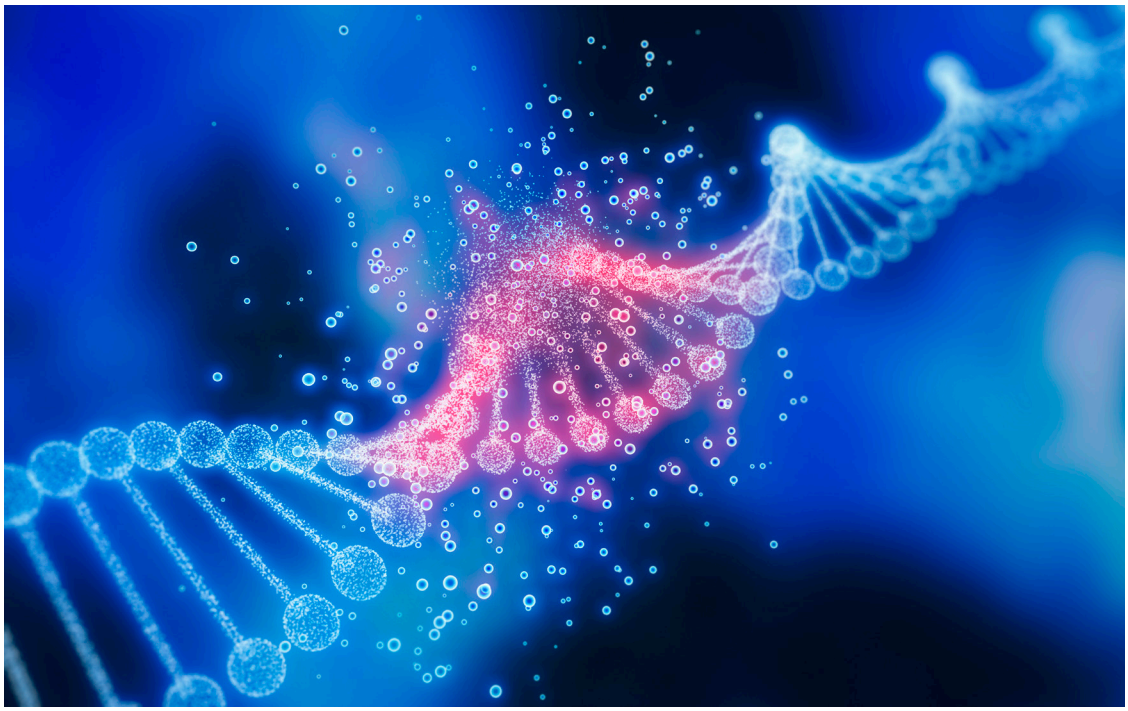
The impact of CRISPR/Cas technology has been mainly in life sciences. Within this domain, most of the projects are in the category of basic research, i.e. research that aims to discover fundamental mechanisms regardless of the potential future applications.

This section illustrates the diversity of the ERC-funded CRISPR/Cas projects in the LS domain and in the context of basic science.

Molecular biology and genetics

While all cells in an organism have nearly the same DNA, they have different functions. The specialisation of cells depends on the regulation of their gene expression, which ensures that each cell type expresses only the genes relevant to its function. The use of CRISPR/Cas has played a crucial role in the study of gene regulation and functional genomics, and the processes of life at the molecular level:

- The project EpigenomeProgramming used the CRISPR/Cas technology, in combination with computational methods, to study the alteration of epigenetically controlled genes in cancer. Led by Christoph Bock at the Research Center for Molecular Medicine (CeMM) in Vienna, one of the outcomes of the project is a patent for a new method of sequencing short fragments of RNA. For more information, visit the project's website.
- The differentiation of a cell into a specific cell type is a necessary step in the development of an embryo. Some of the molecular determinants of this process are still unknown. The DECODE project investigated the architecture of complex tissues by editing the genome of *Arabidopsis* and *Drosophila* in vivo. The researchers used CRISPR/Cas, created an atlas of genetically modified individual cells of these model organisms. More information can be found on the website of this Synergy project, conducted by Michael Boutros at the German Cancer Research Center (DKFZ) in Heidelberg, Wolfgang Huber at the European Molecular Biology Laboratory (EMBL), Jan Lohmann at the Centre for Organismal Studies of the University of Heidelberg and Oliver Stegle at DKFZ and EMBL.

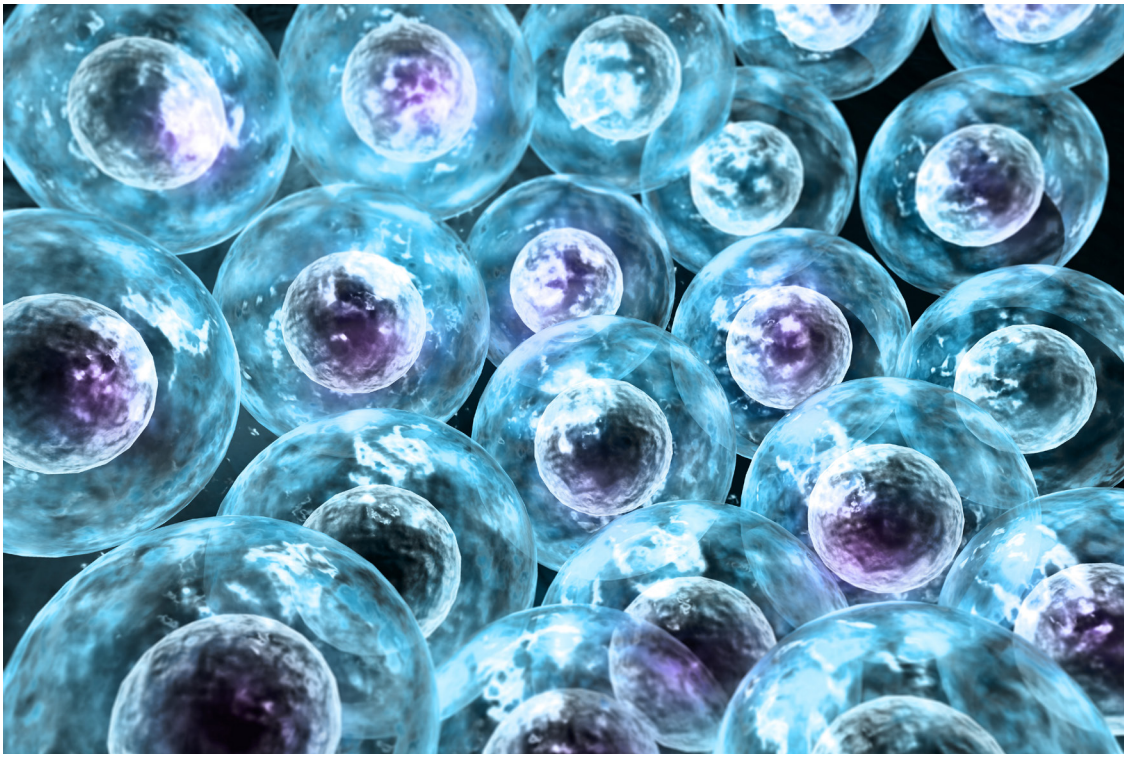


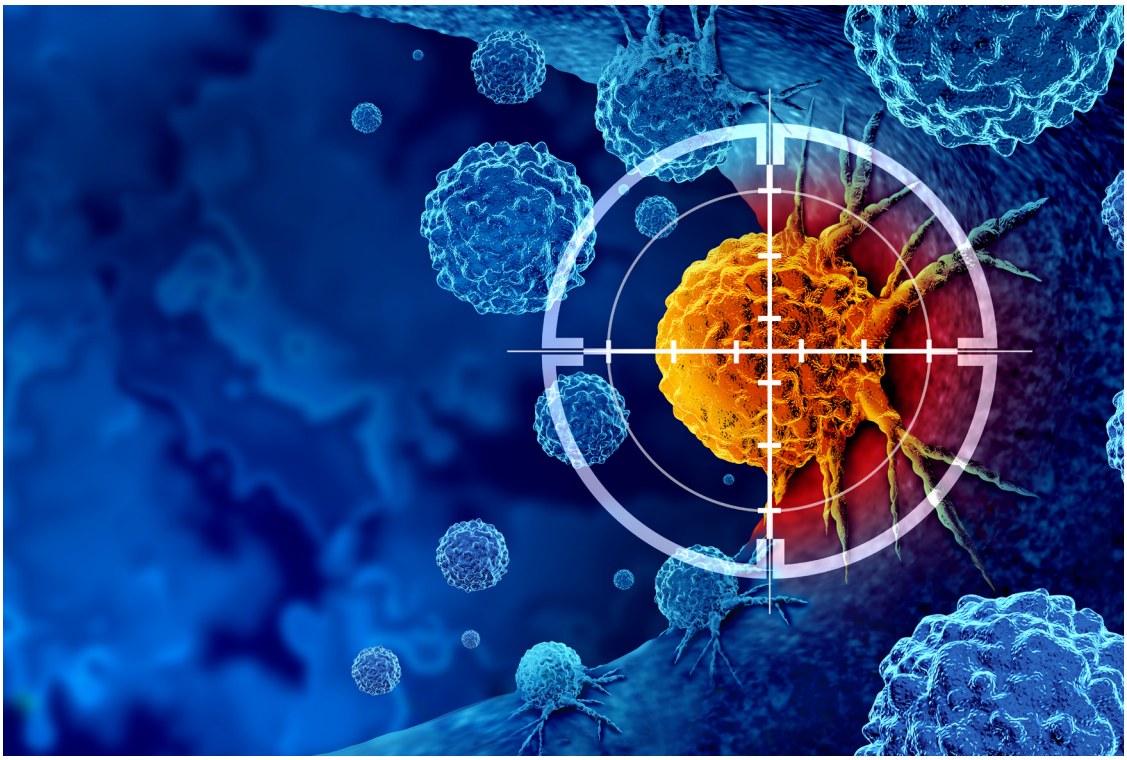
- A multitude of agents and environmental factors can damage DNA, potentially affecting cellular functioning and proliferation. To avoid the harmful consequences of DNA damage, cells have evolved various mechanisms to repair DNA lesions. The project altEJrepair investigated the alternative end joining DNA repair mechanism, using CRISPR/Cas to study the mutational signature associated with this pathway. The long-term goal of the project led by Raphaël Ceccaldi at the Institute Curie in Paris was to find novel drug targets for cancer treatment, and the findings also resulted in a patent application. Read about the project findings here.

Cellular, developmental and stem cell biology

CRISPR/Cas is a technique that is widely used for the characterisation of cellular functions, the formation of tissues and organs, and the identification of the underlying causes of various diseases, including developmental disorders and cancer.

- Led by Barbara Treutlein at ETH Zurich, the project ORGANOMICS has studied cell fate regulation during human cortex development. Her research team has combined CRISPR/Cas, single cell transcriptome sequencing and organoids, which are three-dimensional simplified models of organs. The project findings help to understand the mechanisms underlying neurodevelopmental diseases and the emergence of malformations. Learn more about this on their website.
- Organoids have also been used in MiniBrain to study human brain development and the mechanisms of neurological diseases. Led by Jürgen Knoblich at the Institute of Molecular Biotechnology (IMBA) in Vienna, the research group developed CRISPR-LICHT, a CRISPR/Cas-based assay that was used to investigate microcephaly genes and the mechanisms involved in brain size control. In the associated Proof of Concept project Mini Brains, the researchers used human cerebral organoids to investigate the mechanisms of neurodegenerative and developmental diseases and to test potential therapeutic compounds. For more information visit the group's website.
- Within a tumour, not all cells are alike. Some cells can proliferate, metastasise to other tissues or differentiate. The project TrackingTumorStates, led by Cedric Blanpain at the Université libre de Bruxelles (ULB), aims to understand the different identities and functions of individual cells in squamous cell carcinoma. This information can provide fundamental knowledge for the development of novel cancer therapies. Learn more about this project on the project's website.





Physiology and pathology

The generation of genetically modified models *in vivo* or *in vitro* to characterise the function of a gene/s or to mimic human pathologies can now be conducted rapidly and affordably thanks to CRISPR/Cas. This has paved the way for new approaches to cure human diseases.

- Worldwide, about 240.000 people per year are diagnosed with brain and nervous system tumours. One of the most aggressive brain and lethal tumours is glioblastoma. The project iGBMavatars led by Gaetano Gargiulo at the Max Delbrück Center for Molecular Medicine has developed new genetic tools to identify and characterise different cell types and stages within the tumour and study the contribution of cells of the immune system to cause resistance to current therapies against glioblastoma. Read more on their website.
- ImmunoFit provides insights into the role of metabolism in resistance to immunotherapy against cancer. The project identifies several key genes that provide the tumour microenvironment with immunosuppressive functions that prevent T lymphocytes (white blood cells important in adaptive immunity) from attacking cancer cells. Based on these results, the group led by Massimiliano Mazzone at VIB-KU Leuven Center for Cancer Biology aims to modify T lymphocytes to increase their effector functions and improve their anti-tumour properties. Their research findings have resulted in a filed patent with potential applications for cancer therapy. Read more on their website.
- Coronary artery disease (CAD) is a frequent heart condition. In brief, arteries that supply oxygen to the heart muscle experience a reduced blood flow due to, among other factors, the accumulation of cholesterol plaques. Using cells from human atherosclerotic lesions, the project EnDeCAD has identified hundreds of DNA regions linked to CAD. Interestingly, most of these regions lie outside the coding sequences of the genes and are, in part, responsible for switching them on and off. These investigations have also mapped, at the individual cell level, the cell types enriched in genetic variants linked to CAD, such as endothelial and smooth muscle cells. In the future, the information provided by Minna Kaikkonen-Määttä's group at the University of Eastern Finland could lead to more effective and individualised treatment for CAD.

Basic research on prevention, diagnostics and treatments

Gene editing has an important role in research in clinical settings. For example, inflammatory bowel disease (IBD) is a chronic pathology affecting the gastrointestinal tract due to severe ulceration of the epithelium. IBD affects millions of people across the world (2.5–3 million in Europe) with no medical cure. The following two ERC-funded projects have investigated potential approaches to develop new therapies from two different perspectives using CRISPR/Cas-generated models. The third project uses this technology as a gene expression recorder for diagnostics in the gut:

- Stem cells can generate newly differentiated cells in the resident tissues. This capacity singles these cells out as a prime source for tissue regeneration and transplantation. Led by Kim Jensen at the University of Copenhagen, StemHealth has discovered that adult epithelial intestinal stem cells are re-programmed to a more primitive foetal state upon tissue injury. This reprogramming from adult to foetal confers these stem cells with healing capacity to rebuild the tissue upon damage. Using CRISPR/Cas, these investigators have defined the key genes involved in IBD and have mimicked this pathology in vitro for future clinical applications.
- The intestinal microbiota consists of hundreds of different bacterial species that play an important role in human health. Investigators working on the IMMUNOBIOME project have discovered how stress in the intestinal epithelium, such as IBD, causes an immune and inflammatory response against the microbiota. The group led by Arthur Kaser at the University of Cambridge has identified the factors that drive this inflammatory response which could become new clinical targets for disease treatment. The results of this project include two patents related to potential applications in cancer treatment or infections. For more information about the project, have a look here.
- The physiology of the intestine can be affected by intestinal disease or malnutrition, with possible effects on development, growth, and immunity. Led by Randall Platt at ETH Zürich, the project CRISPRhistory aimed to explore the potential of non-invasive diagnostics of the gastrointestinal tract by microbes, using a technique called ‘transcriptional recording’. This CRISPR-based technique allows the storage of information in living cells, with the conversion of RNA molecules into DNA. These ‘sentinel’ cells can continuously monitor the gut environment and can be used as living diagnostic tools. Learn more about their findings on their website.

Ecology, evolution and biotechnology

CRISPR/Cas technology has proven invaluable in understanding genetic contributions to environmental adaptations, evolutionary processes, and ecological dynamics in natural populations.

- The evolution of multicellularity is one of the major evolutionary transitions. It enabled the emergence of complex organisms such as animals, plants, and fungi. The project Multicellularity investigated the evolutionary and genetic origin of multicellularity in fungi. The research team, led by Laszlo Nagy at the Biological Research Centre of the Hungarian Academy of Sciences, used the CRISPR/Cas system to functionally validate the role of specific genes and regulatory elements. The work contributed to the understanding of the molecular details of fungal multicellularity, which might also have implications in their pathogenicity. Read more about this lab here.
- Antibiotics are an essential tool in medicine for the treatment of infectious diseases. However, their inappropriate use has led to resistance to commonly employed antibiotics in clinical settings. Led by Alvaro San Millán at the National Centre for Biotechnology in Madrid (CNB-CSIC), PLASREVOLUTION has investigated the mechanisms of plasmid–mediated resistance of pathogenic bacteria in hospitalised patients, focusing on fitness cost and adaptation. Using gene editing techniques and whole genome sequencing of enterobacteria clones in thousands of patients, the group has characterised the transmission between and within patients in the gut microbiota. Uncovering these mechanisms of transmission will help provide more educated decisions about antibiotic use in hospitals. For more information, visit the project's website.

Understanding and modifying CRISPR/Cas technology

Some ERC projects have focused on the study of the evolution, molecular mechanisms, and consequences of the CRISPR/Cas system itself. These investigations provide fundamental knowledge and lay the foundations for further technological development.

- CRISPR/Cas evolved as an adaptive immune system in microbes. The immune system is based on the incorporation of short viral DNA sequences in a specific memory locus (CRISPR array), thus forming an 'archive' of invaders. During an infection, this information is transcribed in individual CRISPR RNAs that guide CRISPR-associated

proteins to the invader's DNA, which is then degraded by the Cas nucleases. In the project REMEMBER, the team led by Stan Brouns at Wageningen University has characterised this "memory system" that the cell utilises for defence. Learn more about how these fundamental insights can improve the understanding of the evolutionary relationship between bacteria and viruses on the lab's website.

- Understanding the mechanisms of memory formation in CRISPR also has important applications for genetic engineering. One of the challenges when determining the relationship between a gene and a phenotype is genetic redundancy. In many organisms, two or more genes can have the same function, and therefore inactivating only one of these genes might have no effect on the phenotype. To tackle this problem, the project CRISPRcombo proposed to use CRISPR arrays as new technological developments in genetic engineering. Led by Chase Beisel at the Helmholtz Centre for Infection Research in Braunschweig, this project investigated such CRISPR arrays, with the ultimate goal of developing high-throughput CRISPR-based screens that could target multiple genes at a time. For more information, visit the project's website.
- A downside of the CRISPR/Cas system in genetic engineering is the risk of targeting the wrong genes (off-target events) and causing undesirable effects. The project ZIPgeting used single molecule approaches to study target recognition and to model the potential for off-target recognition. Ralf Seidel and his team from the University of Leipzig described the efficiency and dynamics of this recognition process, which could lead to improved off-target prediction and therefore more reliable genome engineering. Learn more about the project findings here.
- Another possible downside of the CRISPR/Cas system is that, while it protects cells from invaders by degrading their DNA, it might also prevent the acquisition of beneficial genetic traits and thereby reduce genetic diversity. Led by Uri Gophna at Tel Aviv University, the project CRISPR-EVOL investigated the consequences of the CRISPR/Cas system in terms of within-population diversity and quantified the benefit of CRISPR/Cas for both individual cells and entire populations. Learn more about this project at this website.
- CRISPR-associated systems and other genome defence mechanisms were also characterised in the project CRISPR2.0, led by Martin Jinek at Zurich University, using a combination of structural biology and biochemistry. The project provided fundamental mechanistic information on both the CRISPR/Cas system and non-CRISPR systems, that could lead to improvements in genetic engineering technologies. For more information, visit the researcher's lab website.

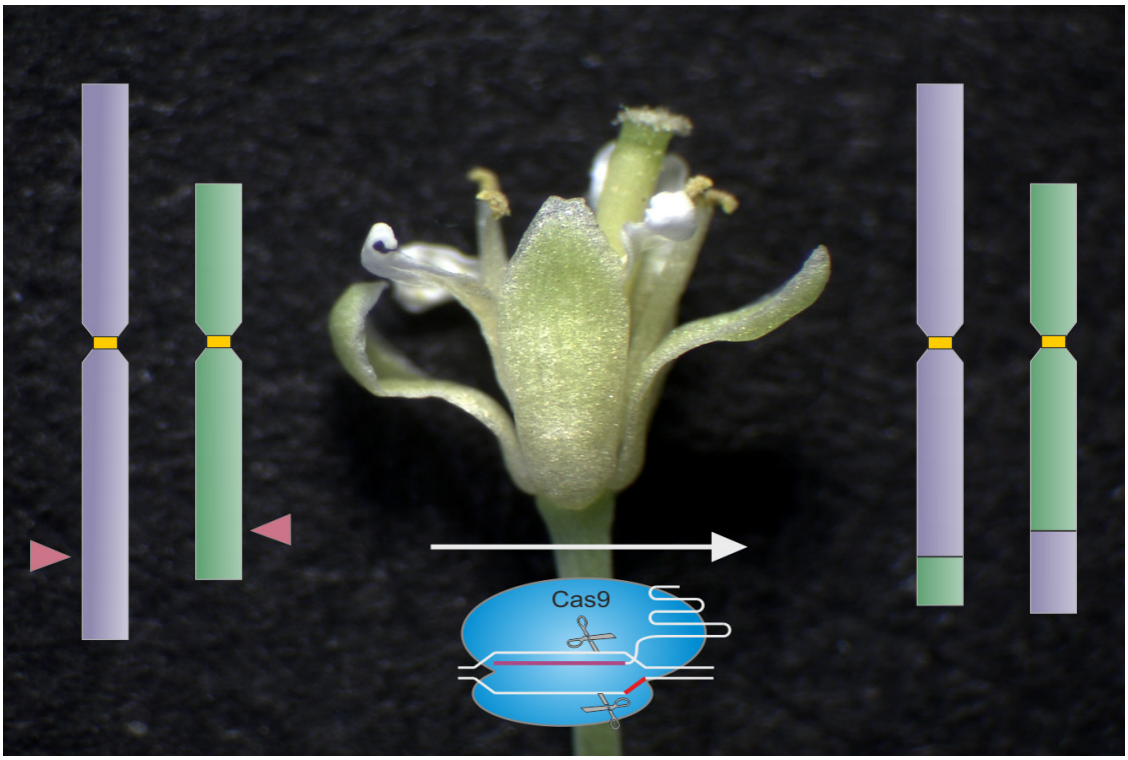
Exploring the ERC-funded CRISPR/Cas project portfolio in applied science

CRISPR/Cas technology has the potential to enhance the competitiveness of life science research as well as the biotechnological and pharmaceutical industries in Europe. This section highlights ERC-funded projects that include innovations in four critical applied areas.

Agriculture and plant biotechnology applications

CRISPR/Cas and gene editing could shape the future of the agricultural industry. ERC-funded research in this area covers a wide range of topics that address critical challenges such as adaptation to climate change and the growth of the world population. Key topics include improving crop yields and their nutritional value, reducing pests and increasing food security.

- Since the invention of agriculture, plant breeding and plant domestication have been used to select and combine advantageous traits in crops, such as disease resistance. However, the inclusion of these features through traditional methods often comes together with unfavourable traits, due to the close position of some genes on a chromosome. The project CRISBREED has developed new techniques to engineer plant breeding based on CRISPR/Cas technology. Led by Holger Puchta at the Karlsruhe Institute of Technology, this project has important implications for crop improvement to overcome the current challenges of global agriculture. Visit the project's website.
- The spider mite *Tetranychus urticae* is a global pest for many different species of plants, including major crops. The aim of POLYADAPT, led by Thomas Van Leeuwen at the University of Gent, has been to understand the molecular adaptation of these small arthropods to pesticides and new hosts. They have developed and filed a patent for a gene editing method for spider mites based on CRISPR/Cas. Learn more about their findings on their website.



© Karlsruhe Institute of Technology - Image from the CRISBREED project.

Microbial biotechnology applications

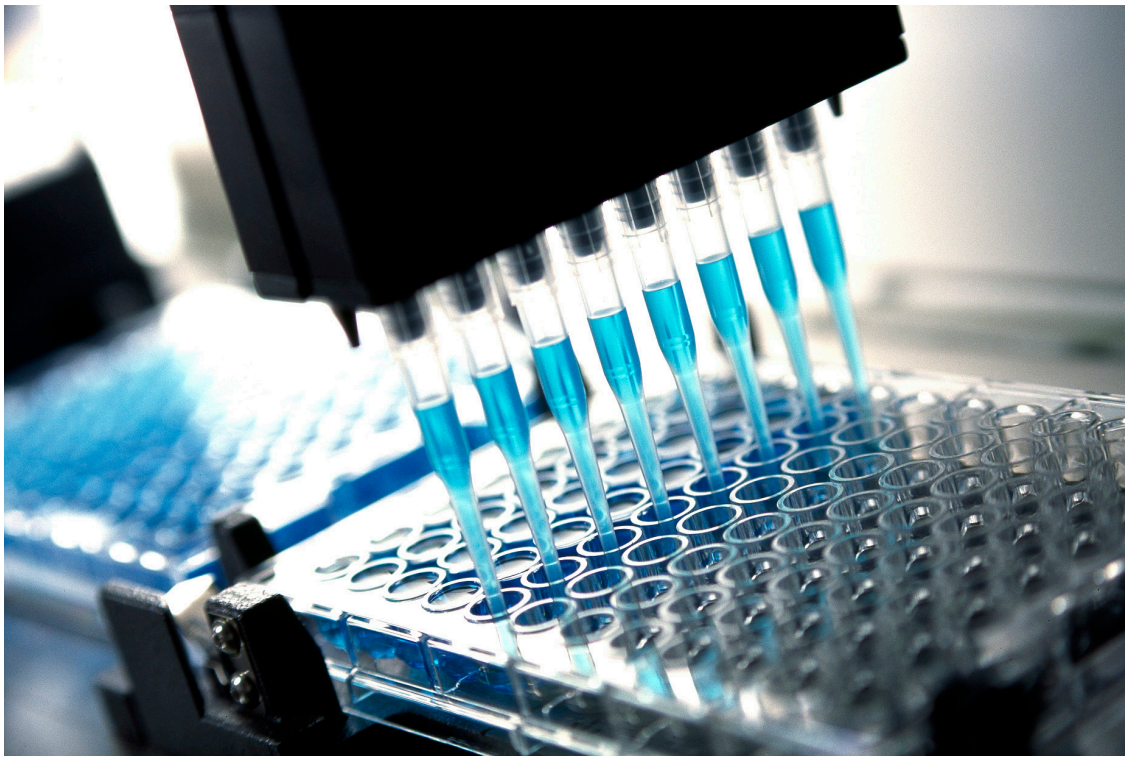
The enhancement and use of microorganisms for industrial applications, such as bacteria, archaea, microalgae, and yeast, leads to innovations in food production, material creation, biotechnological advances, and sustainable practices.

- The SUPERYEAST project, led by Kevin Verstrepen at the VIB-KU Leuven Center for Microbiology, has addressed the repression of respiration in *Saccharomyces cerevisiae*, known traditionally as baker's or brewer's yeast, in industrial settings. In his previous grant, his group discovered that this process limits the fermentation efficiency during the production of beer, bread, bioethanol, and other fermented products. Following this finding, their work led to a patent for a method that uses CRISPR/Cas to overcome this limitation. This innovation has important implications for food technology companies, to increase yeast growth and their industrial productivity. Read more about this Proof of Concept project and the related ERC Consolidator project YEASTMEMORY on their website.
- The YEAST-TRANS project deals with the production of bio-based fuels and chemicals by "microbial factories". Led by Irina Borodina at the Technical University of Denmark, near Copenhagen, this project has studied the transport mechanisms of these compounds in synthetic yeast cells. This knowledge can be applied in industrial settings to engineer more efficient cell factories. Among other outcomes, the group has patented new methods for the biosynthesis of a chemical compound with antioxidant properties, with the use of CRISPR/Cas technology. Learn more about the finding of the project on their website.

Pharmaceutical applications

Drug discovery and development requires several actions, namely performing drug screenings for the identification of potential drug targets, validating those targets, and characterising the mechanisms of action of pharmaceutical compounds in detail. Gene editing tools are extremely useful for this purpose.

- Led by Martin Denzel at the Max Planck Institute for Biology of Ageing in Cologne, the ACUSLABS project has developed a genetic screening platform that can reveal the mode of action and predict potential resistance mechanisms of chemotherapeutic compounds. This technology involves the use of CRISPR/Cas screenings and target validations. In the framework of this Proof of Concept project, the group has established a company that uses this technology. Read more about the related ERC Starting Grant project MetAGEn.



- CIRCACHIP, led by Yaakov Nahmias at The Hebrew University of Jerusalem, is a Proof of Concept project that follows on from the discoveries of a previous ERC Consolidator Grant OCLD. This team has developed a novel platform, a liver-on-a-chip, that mimics the natural oscillations that occur in the human body, called circadian rhythms. They have patented a "bioanalyser" device that is able to capture metabolic oscillations and hormonal and temperature changes. This innovative approach will help to understand how drug toxicity and efficacy depend on the time of day. Visit the researcher's lab website.

Biomedical applications

CRISPR/Cas technology can be applied in healthcare to treat genetic disorders, improve diagnostics, and support preclinical and clinical studies to test the safety and efficacy of new interventions in human subjects.

- Building upon the achievements of the previous ERC Advanced Grant MYCOCHASSIS, led by Luis Serrano at the Center for Genomic Regulation (CRG) in Barcelona, the MycoVAP Proof of Concept aims to engineer bacteria to deliver therapeutic agents locally. This therapy could be employed in the treatment of respiratory diseases, such as pneumonia, which are among the most common causes of severe illness and death worldwide. The group has used a non-pathogenic strain of the small bacterium called *Mycoplasma pneumoniae*, which can break up bacterial biofilms in the lungs. Based on this innovative approach, they have created a start-up company to discover and develop new treatments and vaccines for respiratory diseases. To read more about this, visit the project's website.
- Led by Antonella Consiglio at the Bellvitge Biomedical Research Institute (IDIBELL), near Barcelona, the NeurAntigen Proof of Concept project tackles the issue of the detection of pathogenic antibodies that attack synaptic antigens in autoimmune encephalitis. This is a rare and complex disease that causes brain's inflammation. Using CRISPR/Cas technology, this team has developed a clinical diagnostic kit for the detection of all neural cell surface antigens. Learn more about the findings of the project on their website and in the related ERC Starting Grant[6] PD-HUMMODEL.

- Retinitis pigmentosa is an incurable blindness caused by a dominant mutation in the rhodopsin (RHO) gene, that encodes the rhodopsin protein in the retina. In a previous ERC Starting Grant[7], ALLELECHOKER, this research team led by Enrico Maria Surace at Università degli Studi di Napoli Federico II discovered three modes to repress the rhodopsin gene. Based on these findings, the team conducted preclinical experiments for a novel gene therapy for vision impairment in their Proof of Concept project inSight, resulting in two patents.

In a nutshell

This report surveys the ERC funding projects involving CRISPR/Cas technology, the leading-edge gene-editing technology that is revolutionising biotechnology and life sciences.

Few people could have anticipated that a bacterial immune system could be adapted to modify genes in cells, animals, and plants. The serendipitous discovery by Francisco Mojica of DNA repeats in the genome of a bacterium, found at the Mediterranean Sea coast near Alicante (Spain), laid the foundation for a paradigm shift. This breakthrough exemplifies the importance of exploring curiosity-driven fundamental questions, which can lead to unexpected discoveries, innovation, and technological advances.

The simplicity and low-cost of CRISPR/Cas have propelled this technology as a prime choice for introducing changes in DNA. We are in the middle of a “revolution” with exciting and promising discoveries. The over 1000 ERC-funded projects identified in this analysis, are a clear demonstration of the profound impact of this technology.

Remarkably, the outcomes of ERC-funded research involving CRISPR/Cas technology extend well beyond theoretical advances. This is shown by more than 30 projects with associated patents and the creation of spin-off companies, as mentioned in some of the highlighted projects above. Investments in curiosity-driven science can thus lead to significant impact, not only by advancing our understanding of the living world but also for fostering practical applications and delivering solutions with far-reaching scientific and technological benefits.

Acknowledgments

We acknowledge the members of the ERCEA Scientific Department "CRISPR/Cas and gene editing" team for their work (Marta García Juan, Alice Bolner and Ignacio Moreno de Alborán from the ERC Life Sciences Unit), who were led for this report by Jaime Gómez Ramírez from the Scientific Impact and Feedback to Policy (F2P) Sector in the ERCEA.

We would like to thank Dirk Inzé, member of the ERC Scientific Council, for his guidance and enthusiasm leading up to the publication of this report. We would also like to thank Eleni Zika, Head of the F2P sector for her guidance, and the ERCEA F2P network for their valuable feedback and support, with special thanks to our colleagues from the ERCEA scientific department and Inge Ruigrok from the Communication Unit. Finally, we would like to thank Dimitra Zagoura, from the European Commission's DG Research and Innovation Health Directorate, for her insightful comments.

Under the Horizon Europe programme, the European Commission has delegated to the ERC Executive Agency (ERCEA) the task of identifying, analysing, and communicating policy relevant research results to the European Commission. The ERCEA has developed a Feedback to Policy (F2P) framework to guide these activities adapted to the ERC as a bottom-up funding programme. This report is part of a series on ERC-funded frontier science, that address acute societal, economic, or environmental challenges and thus their contributions towards key EU policy goals. This F2P series does not offer any policy recommendations. For more information on ERC Frontier Research visit the website.

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Endnotes

1 The European Commission proposal on plants obtained by certain new genomic techniques (NGTs) and their derived food and feed products is currently under debate within European Institutions. The European Biotech Act, set for 2025 aims to facilitate the transition of biotech innovation from the laboratory to the market. This initiative is part of a new Strategy for European Life Sciences, designed to support green and digital transitions and foster the development of high-value technologies such as CRISPR/Cas and others.

2 According to a study published by the European Commission on 29 April 2021 regarding the status of New Genomic Techniques under Union law, there is confirmed interest in research on new genomic techniques in the EU.

3 The Commission recently reaffirmed the importance of biotechnology for the EU's competitiveness and strategic autonomy, and has proposed a series of targeted actions to boost biotechnology and biomanufacturing in the EU in the communication "Building the future with nature: Boosting Biotechnology and Biomanufacturing in the EU".

4 Article 18 of the Horizon Europe Regulation excludes from funding research activities modifying the human germline, which is one of the most controversial potential applications of CRISPR/Cas technology. An ethics appraisal process evaluates other high-risk applications of CRISPR/Cas technology, ensuring adherence to established ethical and regulatory principles, as well as relevant provisions and guidelines in other legislative acts with implicit references, such as EU Directive 2010/63/EU (on the protection of animals used in scientific research, including research using genome editing technologies) or Regulation EU 2017/746 on in vitro diagnostic medical devices. The ethics review process also keeps up with the changing legislative landscape through the monitoring of projects.

5 The ERC panels are as follows LS1: Molecules of Life: Biological Mechanisms, Structures and Functions; LS2: Integrative Biology: from Genes and Genomes to Systems; LS3: Cell Biology, Development, Stem Cells and Regeneration; LS4: Physiology in Health, Disease and Ageing; LS5: Neuroscience and Disorders of the Nervous System; LS6: Immunity, Infection and Immunotherapy; LS7: Prevention, Diagnosis and Treatment of Human Diseases; LS8: Environmental Biology, Ecology and Evolution; LS9: Biotechnology and Biosystems Engineering; PE3: Condensed Matter Physics; PE4: Physical and Analytical Chemical Sciences; PE5: Synthetic Chemistry and Materials; PE7: Systems and Communication Engineering; PE8: Products and Processes Engineering; SH4: The Human Mind and Its Complexity. Learn more in the Panel Structure for ERC calls document.

6 The original ERC Starting Grant PD-HUMMODEL was from FP7.

7 The original ERC Starting Grant ALLELECHOKER was from FP7.

Luxembourg: Publications Office of the European Union, 2024

PDF: ISBN 978-92-9215-122-5 • doi: 10.2828/2570980 • JZ-01-24-001-EN-N

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