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European Commission

CORDIS Results Pack on

frontier research for cancer

A thematic collection of innovative EU-funded research results

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Supporting better understanding of cancer through EU research

Research and Innovation

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Editorial

Supporting better understanding of cancer through EU research

Cancer represents one of Europe's most pressing public health concerns. The European Research Council plays a pivotal role in advancing our understanding of cancer development and progression through its support for curiosity-driven research, thereby paving the way for innovative treatments. This Results Pack highlights nine frontier research projects dedicated to advancing cancer research.

In 2020, 2.7 million people in the European Union were diagnosed with cancer, and a further 1.3 million lost their lives to the disease. Projections indicate that cancer cases will increase by 24 % by 2035, potentially making it the leading cause of death in Europe.

Recognising the magnitude of this challenge, the European Commission has designated cancer as one of its five EU Missions, guiding research and innovation funding. The Mission aims to enhance our understanding of cancer, promote improved prevention and early detection, improve diagnostic and treatment methods, and boost quality of life for both patients and their families.

Europe's beating cancer plan will direct EUR 4 billion into research efforts combined with new forms of governance and collaboration, supported by the EU4Health programme.

The European Research Council (ERC) funds curiosity-driven research using scientific excellence as the sole criterion to award the grants. And by doing so, it plays an important role in creating new knowledge called for in this important policy area.

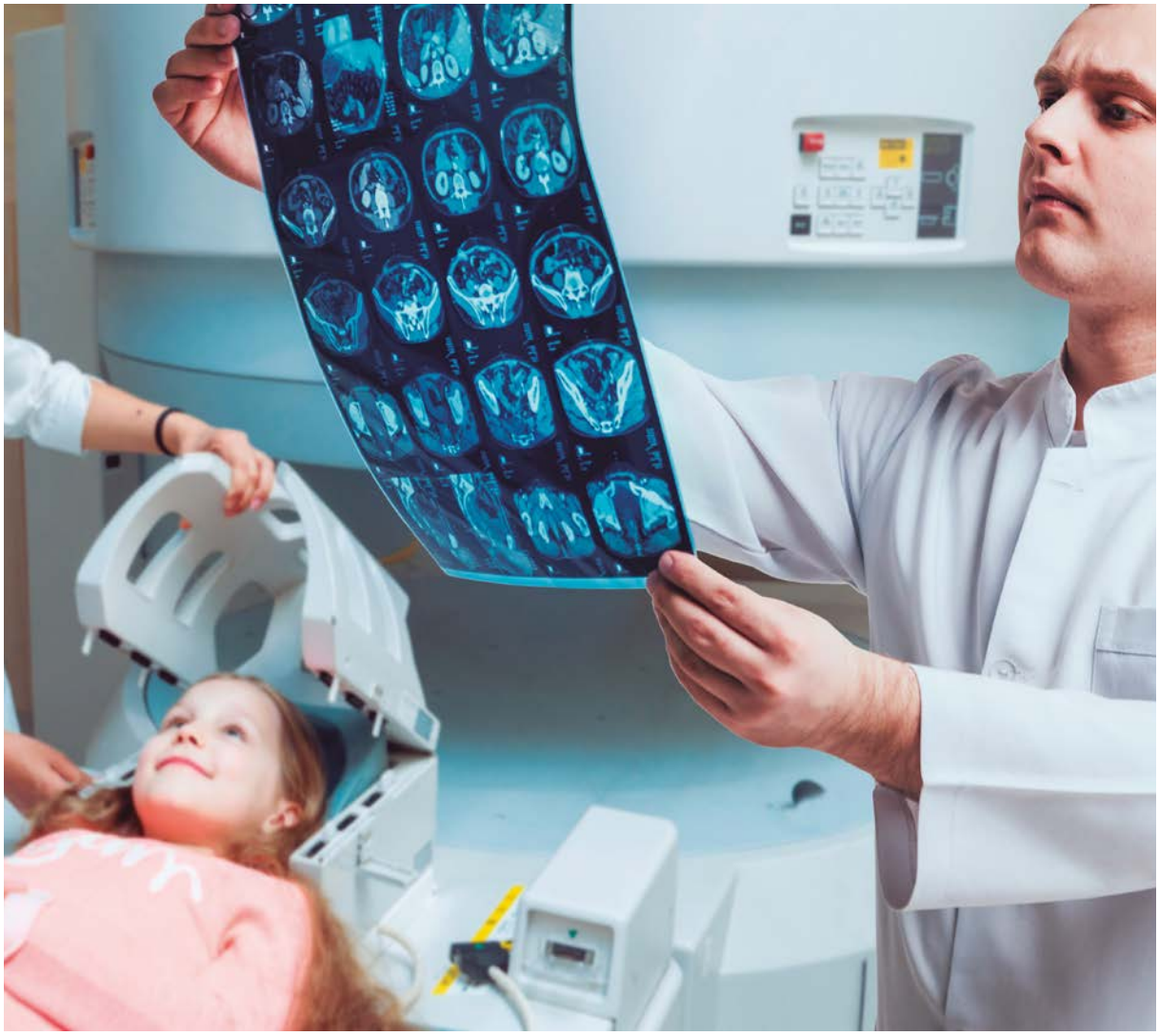
Health research features prominently in the ERC's project portfolio. An analysis of the research funded by the ERC under the Horizon 2020 framework programme (2014-2020) revealed that approximately one third of projects funded are connected to various fields of health research. The report identified a total of 2 281 projects, which collectively received grants amounting to EUR 4.6 billion and engaged thousands of researchers from EU Member States and Associated Countries.

The ERC provides support to a wide range of cancer research projects, encompassing cell and molecular biology, immunology and genetics, as well as the examination of tumour progression and the development of drugs and their delivery methods. While the majority of these projects are rooted in the life sciences, a substantial number also come from the physical sciences and engineering field as well as the social sciences and humanities. This diversity illustrates the breadth of the science supported by the ERC in the field of cancer research, highlighting the advantages of adopting a multidisciplinary approach.

These ERC-funded projects are contributing to the discovery of new insights into cancer, informing prevention strategies, advancing our capacity for early detection, and shaping the development of effective treatments for those living with the disease. Collectively, the curiosity and innovative approaches have the potential to extend the lives and well-being of individuals both within Europe and around the globe, helping people to lead longer and healthier lives.

Tracing brain cancer's 'cell of origin' points to pre-birth

By mapping the development of cancers, the EU-funded BRAIN-MATCH project uncovered new evidence for the hypothesis that brain tumours originate during embryonic development, opening up new avenues for treatment and diagnosis in the process.



Compared to other cancers, brain tumours remain stubbornly difficult to treat. The blood-brain barrier prevents most therapeutics from reaching the brain, and as an immune-privileged organ, it is particularly difficult to leverage the immune system's own defences in this area.

In addition, the brain is vulnerable to long-term damage and life-threatening complications, requiring studies and treatments to be undertaken with caution.

This work suggests cancerous cells hijack properties of normal cells during the embryonal period, rather than after birth.

"Brain tumours are also extremely diverse, with probably around 200 different types, making each very rare," says Stefan Pfister, project coordinator of BRAIN-MATCH, a project funded by the ERC. "Crucially, the fact that the cell of origin is also often unknown further impedes the development of specific treatments."

To help identify the cell of origin that gives rise to brain tumours, BRAIN-MATCH developed atlases to compare normal brain development in embryos and children with the molecular profiles of various brain tumour types in children, taken from data sets containing over 100 such tumours.

"This told us about the timing and mechanisms by which the tumour hijacks normal processes, preventing it from being recognised by the body as 'foreign' and so a threat," explains Pfister, from the German Cancer Research Center, the project's host institution. Pfister is also affiliated with the Hopp Children's Cancer Center Heidelberg and Heidelberg University Hospital in Germany.

Tracing the origin story

BRAIN-MATCH was inspired by the long-standing – but still unproven – hypothesis that childhood brain tumours are embryonal in origin, and may even be initiated in early pregnancy.

Since the cellular origin of most brain tumours remains unknown, they are hard to model and to develop targeted treatments for, as these treatments must distinguish between the embryonal properties of tumour cells and normal differentiated brain tissues.

The BRAIN-MATCH team used single-cell transcriptome and ATAC sequencing to analyse frozen brain tissue samples, starting at the embryonic stages. This resulted in large atlases of normal and cancerous brain development, specifically the cerebellum and brainstem, at single-cell resolution and characterising several hundred thousand cells. This was complemented by spatial transcriptome analyses, a molecular profiling method which can reconstruct tissues at the cellular level.

"We were surprised how little is known about some cell types in the normal developing human brain, especially in the cerebellum and brainstem, where the majority of childhood brain tumours arise," says Pfister.

Analysis of both the cellular composition and differentiation of normal and tumour tissues highlighted commonalities and differences, ultimately pinpointing the cellular origin of various tumour types.

"A key finding was that many tumours show extensive differentiation, from very primitive progenitor states all the way to differentiated cells, a progression very similar to normal cells," notes Pfister. "This suggests cancerous cells hijack properties of normal cells during the embryonal period, rather than after birth." He adds that the findings provide attractive targets for tissue-specific and time-bound treatments, minimising side effects.

These properties could also help reliably identify tumour cells or nucleic acids in the cerebrospinal fluid or blood, enabling clinicians to make a diagnosis without operations or biopsies. It would also offer an effective means to monitor the response of patients to treatment.

A rich therapeutics resource

There is currently little financial incentive for industry to develop specific therapeutics for rare diseases such as childhood brain tumours. In addition, most drugs that could potentially be repurposed for these cancers are designed specifically not to penetrate the brain.

"While therapeutic developments will probably need novel financing arrangements, our data offers a rich resource to help identify and prioritise therapeutic targets for these rare diseases. Our data set of normal human brain development is also relevant for research fields beyond cancer, such as cognitive health, brain injury and neurodegeneration," concludes Pfister.

After the relevant publications, the project's brain atlases will be made available to researchers, with another brainstem atlas currently under development.

Meanwhile, a paper on mouse atlases has already been published in 'Science', with another on the human cerebellum

pending. Some of the results have also been recently published in 'Neuro-Oncology'.

The team is now focused on functionally validating the tissue specificity of the targets identified and their role in killing tumour cells. Various tumour types will also be modelled to understand their mechanisms of resistance during their evolution.

PROJECT
BRAIN-MATCH – Matching CNS Lineage Maps with Molecular Brain Tumor Portraits for Translational Exploitation

COORDINATED BY
German Cancer Research Center in Germany

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/819894

PROJECT WEBSITE
brain-match.org/

Advancing immunotherapy to solve the colorectal cancer paradox

New research by the EU-funded EPIC project opens the door to personalised combinations of immunotherapy and conventional drugs that can tackle hard-to-treat tumours.

For many types of cancers, immunotherapy has emerged as a powerful tool for treating the disease. The exception is colorectal cancer (CRC), a disease that affects 1.4 million people every year.

"We know that CRC is under the surveillance of the immune system, yet for some reason it is largely resistant to immunotherapy," says Zlatko Trajanoski, a researcher at the Medical University of Innsbruck. "This is what we in the medical field refer to as the CRC paradox."

The organ-on-a-chip

EPIC's researchers wanted to know if there was a way to override this resistance using conventional drugs, sensitising tumours to immunotherapy. The goal of the project, which received support from the ERC was to identify the root cause of CRC's resistance to immunotherapy. Based on this, researchers aimed to develop personalised models for predicting a CRC patient's response to a combination of immunotherapy and conventional drugs such as chemotherapeutics or targeted drugs.

We know that colorectal cancer is under the surveillance of the immune system, yet for some reason it is largely resistant to immunotherapy.

To achieve this, the project used patient-derived organoids: simplified, 3D versions of organs, produced in vitro, that replicate the organ's structural and biological complexities. "As these 3D organ-like structures have the same genetic footprint as a patient's tissue, they let us study the effects of various drug combinations," explains Trajanoski, who served as the project coordinator.

Using a process called functional precision profiling, the organoids were subjected to various drugs. Researchers measured the impact a drug had on intracellular signalling – the biological process that cells use to communicate. "While this signalling can regulate or even prevent the growth of cancer cells, sometimes these messages get lost," adds Trajanoski. "When this happens, cancer cells can rapidly grow, possibly resulting in a tumour."

Precision cancer immunotherapy

Researchers identified specific combinations of different drugs that have a profound impact on cell signalling. Whether that impact is beneficial or detrimental is both patient- and drug-specific. It can also be affected by the plasticity and non-genetic heterogeneity of the tumour.

According to Trajanoski, this could pave the way for informing precision cancer immunotherapy. It also opens the door to cancer therapy based on a combination of immunotherapy and conventional drugs tailored to the individual patient.

While the project's work represents an important breakthrough in the treatment of CRC, it only scratches the surface of what's possible. EPIC's researchers produced a vast amount of data on cell signalling, nearly 90 % of which was not fully analysed. The project has made this data publicly available, and hopes that other researchers will be able to apply emerging methods, such as artificial intelligence, to extract new insights.

Furthermore, as the EPIC project only used tumour cells, additional research is needed to test the approach in a more complex system. Doing so will provide additional information on the contribution of other cell types, including fibroblasts and immune cells.

"We've provided novel biological insights into CRC and have laid the groundwork for creating patient-specific treatment plans," concludes Trajanoski.

PROJECT
EPIC – Enabling Precision Immuno-oncology in Colorectal cancer

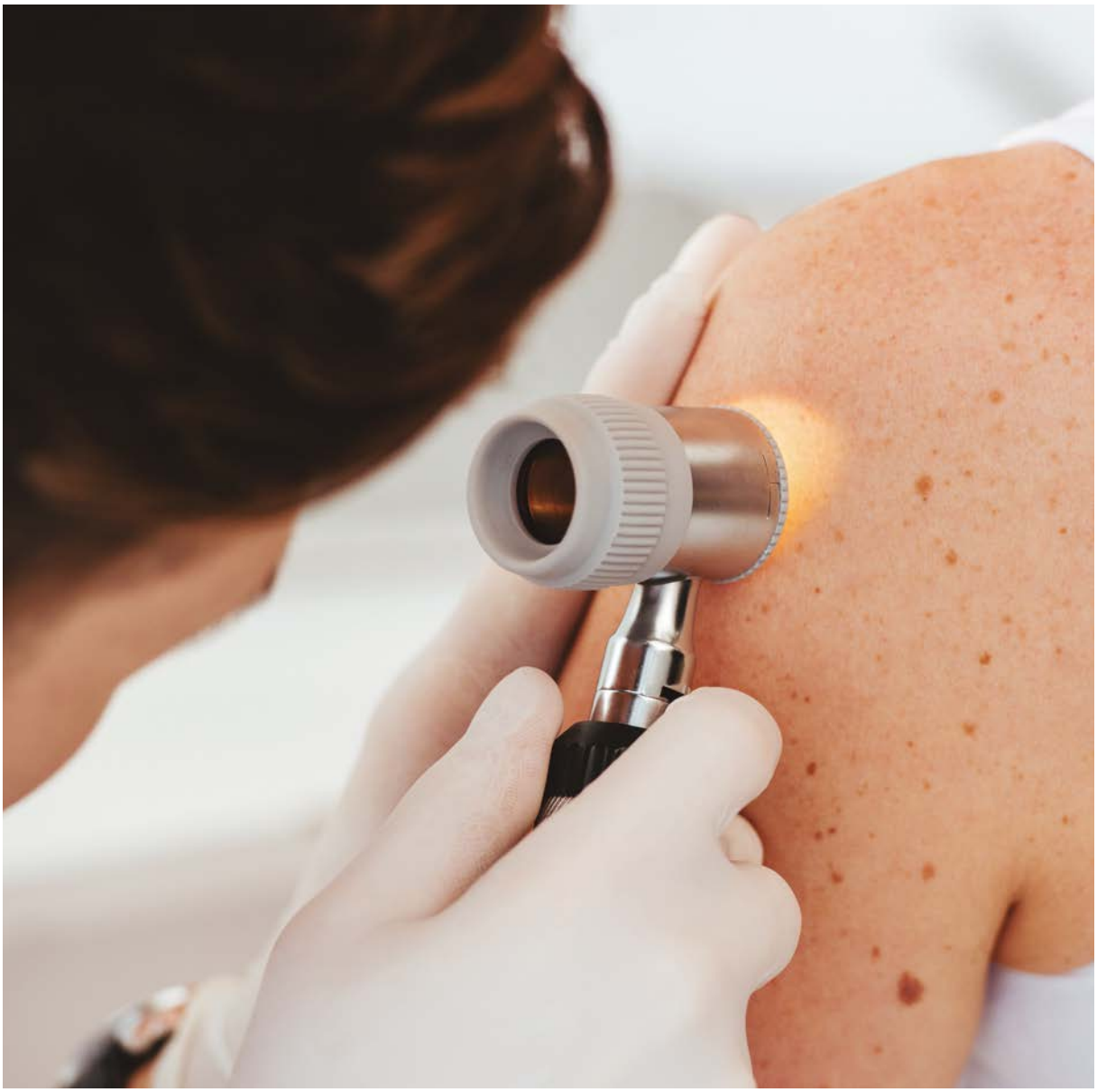
COORDINATED BY
Medical University of Innsbruck in Austria

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/786295

Melanoma insights could hold benefits for all cancers

The EU-funded MEL-Interactions project demonstrated new tools and experimental models to reveal the genetic, protein and T-cell interactions driving melanomas, advancing personalised cancer treatments.



Malignant melanomas are the main cause of death from skin cancer, with 132 000 deaths annually worldwide. While treatment typically involves surgery, there is a growing interest in the potential of immunotherapies.

Taking melanoma as a model cancer system, the MEL-Interactions project, which was funded by the ERC, explored key interactions amongst genes and signalling proteins, as well as between melanoma cells and immune cells, to identify opportunities to improve immunotherapies.

"Our work has already identified promising therapy targets called neoantigens. With several ready for clinical trials, this could benefit around 300 000 melanoma cancer patients per year," explains Yardena Samuels, the project's coordinator.

The team's genomics data, submitted to the open-science database COSMIC, has already allowed other teams to apply techniques such as machine learning in the pursuit of drug targets to treat a range of cancers.

Melanoma as a model system

When Samuels set up her lab at the Weizmann Institute of Science 15 years ago, she decided to investigate the little known genetic basis of melanomas. Since then, her team has built a highly annotated tumour bank of over 100 samples. This allowed the team to publish the first melanoma whole exomes, followed by whole genomes.

This databank also provided the foundation for Samuels to investigate the potential of immunotherapies. "Melanomas are one of the most highly mutated solid cancers," says Samuels. "As mutations are key to immunotherapies, by chance I had chosen a highly relevant cancer type for research into this field."

From genes to pathways

Thanks to information made publicly available through the landmark Cancer Genome Atlas programme, to which Samuels contributed, it is known that melanoma mutant genes divide into four main subgroups: BRAF, RAS, NF1 and triple wild-type.

"There had already been a breakthrough with a small molecule inhibitor for BRAF, mutated in 50 % of melanomas, but within six months patients developed resistance," adds Samuels.

Consequently, Samuels focused on mutation pathways to spot commonalities between subtypes. The majority of tumours harbour a mutation in the same pathway (MAP kinase), which could explain why the mutations are mutually exclusive – pointing to possible drug targets that could treat all subcategories.

"The more we know about these pathways, the more we can target tumours in a highly personalised way," explains Samuels. Bioinformatics pathway analysis on different mutations helped the team prioritise which to study. The mutant was then cloned and expressed in cells to study outcomes, such as its effect on tumour cell growth and invasion rates.

Neoantigens as immunotherapy targets

Samuels' colleague Steven Rosenberg had established protocols for a cell therapy that uses tumour-infiltrating lymphocytes (TILs) or white blood cells, to treat solid tumours. While showing promise, it remained unclear what spectrum of antigens the TILs target.

MEL-Interactions provided important evidence that the TILs target not only tumour-associated antigens but also tumour-associated neoantigens – proteins arising from mutations and harboured by the tumours themselves.

Samuels' team identified the neoantigens involved and was the first to use immunopeptidomics to identify presented neoantigens that would trigger an immune response. After identifying these responsive T-cells, the receptor specific to this neoantigen could be cloned.

"If we can engineer the T-cells to recognise the neoantigen on the target cell, then immunotherapy will prove more powerful than the current 20-40 % response rate for cutaneous melanoma," Samuels says.

Our work has already identified promising therapy targets called neoantigens; this could benefit around 300 000 melanoma cancer patients per year.

Personalised cancer treatment

The team's work is applicable to a range of cancers, and neoantigen targets have already been identified for prostate, breast and colorectal cancers, among others.

When building a library of inhibitors or immunotherapy tools for personalised treatment targets, the project has demonstrated the value of investigating low, as well as high, incidence mutations.

But questions remain. "It isn't clear which mutated proteins drive the cancer process, as opposed to being simple passengers, and not every neoantigen is a good target. We still need to find ways to induce the presentation of neoantigens in cancers with low mutations to create treatment targets," Samuels notes.

PROJECT
MEL-Interactions – An integrative approach for the exploration of melanoma genetic and immunological interactions

COORDINATED BY
Weizmann Institute of Science in Israel

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/770854

PROJECT WEBSITE
weizmann.ac.il/mcb/Samuels

New tools to better understand and fight paediatric sarcomas

The EU-funded PedSarc project delivered a better understanding of the molecular processes responsible for a common childhood cancer, offering new targets for potential therapies.

Sarcomas are malignant tumours that develop in bone or connective tissue. They can occur in adults, but are more frequent in children and young adults. "There are many challenges to treating these types of tumours," explains PedSarc project coordinator Ana Banito from the German Cancer Research Center. "For one thing, there are many different subtypes. What works for one subtype may not be suitable for another."

Each sarcoma subtype is also relatively rare, so the collection of sufficient patient samples and data has long been a challenge. As a result, scientists have found it difficult to fully understand the molecular pathways that promote sarcoma development.

The PedSarc project, funded by the ERC, set out to address these shortcomings. "We had two main aims," says Banito. "First, to understand how specific genetic alterations give rise to sarcoma. And second, to develop more flexible mouse models that will allow us to test specific biological hypotheses and therapeutic strategies."

Specific genetic alterations identified

At the molecular level, the project used several tools – such as the gene editing tool CRISPR – to study gene regulation and gene inactivation. The project team was able to identify specific gene fusions that could play a role in the development of paediatric sarcomas.

The project achieved a significant breakthrough with its work on a specific protein, SS18-SSX, which gives rise to synovial sarcoma, the second most common malignant soft tissue tumour in children and young adults. Banito and her team were able to identify the molecular mechanisms of protein-gene interaction that enables it to regulate specific genes to promote cancer. "The goal now is to find out how to disrupt this activity, by inhibiting this gene-protein interaction," adds Banito.

Testing specific therapeutic strategies

The PedSarc project also focused on new developing methods for investigating sarcomas in vivo. For this, a new way of delivering transposon vectors into muscle tissue was pioneered in mice. These fragments of DNA mediate the insertion of specific mutated genes into the genome.

By applying a small electric pulse, the team was able to insert these fragments to mimic gene fusion activation in normal cells, revealing if and how these fusions give rise to sarcomas.

"The mouse model development in this project has been especially innovative," says Banito. "It enables us to rapidly test several genetic alterations in mice with intact immune systems, and potentially use it as a model to test novel therapies including immunotherapies. We are currently preparing a paper describing these models, and will make this available as a resource for the scientific community."

New tools to overcome sarcoma

Banito believes that the project's two-step approach – of better understanding how genetic alterations give rise to sarcoma, and developing more flexible mouse models – has helped to shine a light on how sarcomas arise.

The hope is that over the longer term, the project's results will give rise to new treatments that can benefit patients. For synovial sarcoma, the project has already helped to identify a key molecular mechanism for new therapies to target. The new mouse models should also enable scientists to test many more therapeutic strategies, and answer more questions concerning sarcoma.

We are still a long way from finding treatments for all sarcoma subtypes, but now we have more tools to overcome this challenge.

"Our mouse models are already being used to test immunotherapies, and we plan to use them in subsequent studies to test additional therapeutic strategies," notes Banito. "We are still a long way from finding treatments for all sarcoma subtypes, but now we have more tools to overcome this challenge."

PROJECT
PedSarc – Targeting genetic and epigenetic mechanisms in pediatric sarcomas

COORDINATED BY
German Cancer Research Center in Germany

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/805338

Understanding the mysterious cell bodies that help cure leukaemia

By understanding how blood cancers respond to treatments, the EU-funded PML-THERAPY project is helping researchers to optimise existing therapies and discover new ones.

Acute forms of leukaemia can progress quickly and aggressively. In these cases, abnormal white blood cells multiply rapidly, enter the bloodstream and crowd out healthy blood cells, with the condition demanding immediate treatment.

The good news is that the genetics of leukaemia are more understandable to scientists than those of solid tumours. This has led to the development of numerous targeted therapeutic options in addition to chemotherapy and stem cell transplants.

"From our understanding of disease pathogenesis, we can optimise existing therapies," explains PML-THERAPY project coordinator Hugues de Thé from France's National Institute of Health and Medical Research (Inserm).

"In particular, my research group is interested in identifying the cellular and biological bases for how these cancers respond to treatments."

Therapeutic responses of acute myeloid leukaemia

In the PML-THERAPY project, funded by ERC, de Thé and his team are focusing specifically on the therapeutic responses of acute myeloid leukaemia (AML). Broadly speaking, AML is an aggressive form of leukaemia that targets the monocyte or granulocyte cells.

The project builds on the findings of STEMAPL, a previous project funded by the ERC which successfully identified the molecular basis for therapeutic responses to a specific form of AML called acute promyelocytic leukaemia (APL).

"Here, we were able to unravel the mechanisms underlying these cures, and our findings were subsequently validated in patients," says de Thé. "Targeted therapies now allow us to cure virtually all APL patients."

A key feature of the validated APL cures was their ability to activate promyelocytic leukaemia (PML) nuclear bodies. These subnuclear structures, 0.1 to 1.0 micrometres in diameter, are found in most cell lines and many tissues, but many aspects of their purpose and function remain unclear.

"The primary objective of our current ERC project is to decipher whether PML nuclear bodies play any role in the response of other forms of leukaemia to therapy," explains de Thé.

Evidence implicating PML nuclear bodies

To achieve these aims, the project combined basic biochemistry, cell biology and experimental therapeutics. Mice models were developed to help the team compare therapeutic responses in settings where PML nuclear bodies could no longer form.

"These mysterious nuclear domains have fascinated cell biologists for years, and still remain quite a challenge," adds de Thé.

In particular, the project team investigated therapeutic reactions in two conditions. These were myeloproliferative neoplasms (in which the bone marrow produces too many red blood cells, white blood cells, or platelets) and AML with mutations in the gene NPM1c.

"Without going into too much technical detail, we found evidence that implicates PML nuclear bodies in therapy response in both conditions," notes de Thé. "From this knowledge, we have been able to elaborate, in mice models, new therapeutic approaches based on novel drug combinations."

New treatments and drug combinations

Unravelling the molecular mechanisms associated with therapeutic responses will help to foster new treatments, notably novel drug combinations. The development of such effective, non-invasive therapies will bring clear benefits to cancer patients, and save healthcare systems money by transitioning treatments from long-term care towards cures.

"Our studies imply a much broader role for PML in therapy response than was initially anticipated," remarks de Thé. "This justifies the emphasis we have put on PML biology, as it may yield further therapeutic approaches."

The PML-THERAPY project runs until March 2024, and discussions are currently ongoing regarding the possibility of clinical trials. "I am confident these will happen, because the biological rationale is very strong," says de Thé.

Targeted therapies now allow us to cure virtually all acute promyelocytic leukaemia patients.

PROJECT
PML-THERAPY – Harnessing PML nuclear bodies for leukaemia THERAPY

COORDINATED BY
National Institute of Health and Medical Research in France

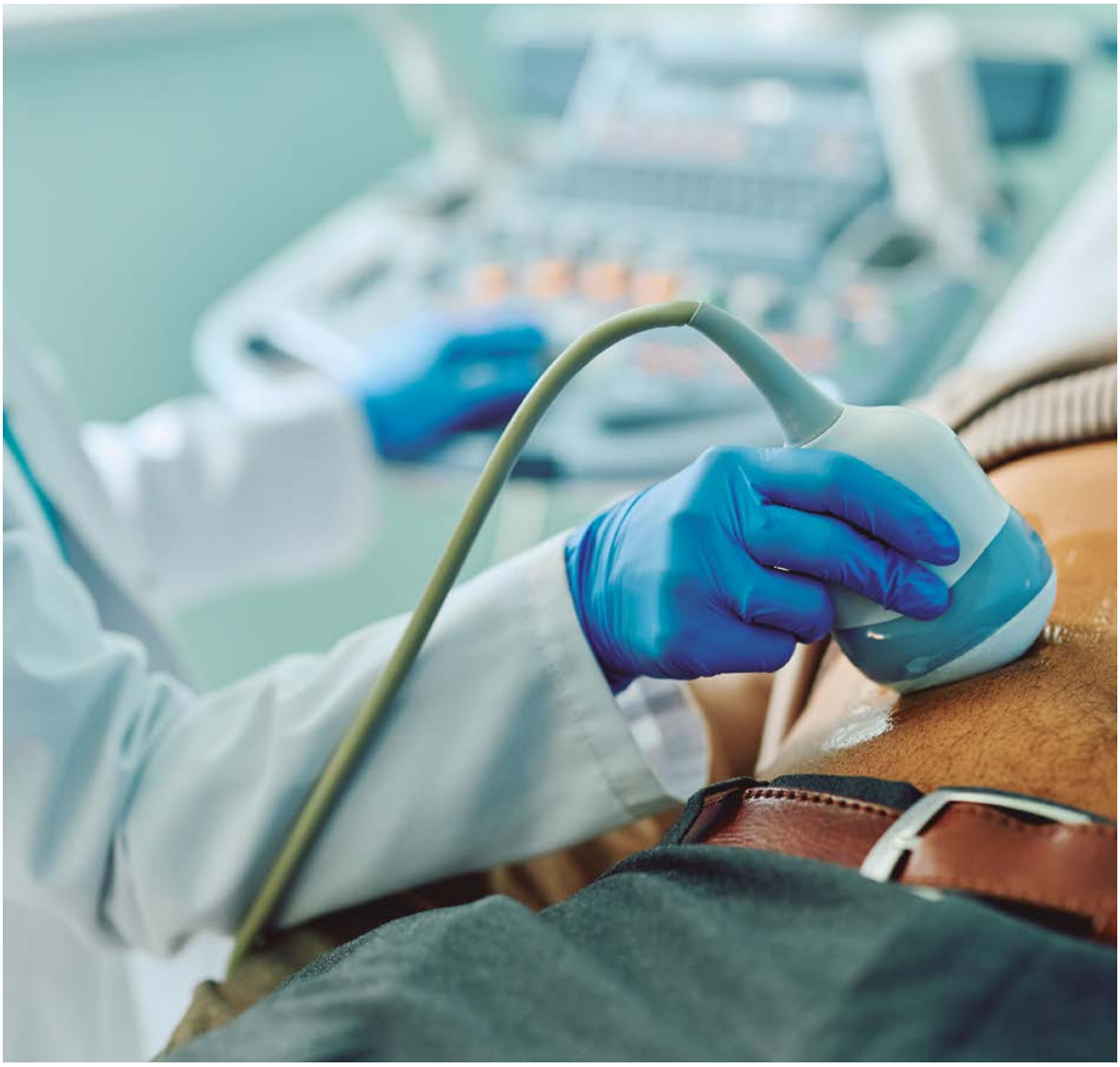
FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/785917

PROJECT WEBSITE
gencelldis.fr/h-de-the-team

Suppressing cancer from within using microRNA

By identifying molecules that can stimulate the production of tumour-suppressing microRNAs in the body, the EU-funded RxmiRcanceR project aims to open the door to a new generation of cancer therapies.



Cancer is inextricably linked to genetics, and in most cases, to genetic mutations that occur during life. "These genetic mutations alter the behaviour of cells," says RxmiRcanceR project coordinator Eithan Galun from the Hadassah Hebrew University Hospital of Jerusalem in Israel. "This usually involves multiple genetic changes in the tissue, which leads to cancer."

The RxmiRcanceR project, funded by the ERC, sought to treat cancer at the genetic level. This is hugely challenging: in the example of pancreatic cancer, it is common to find 60 different mutations in a single case.

"This helps to explain why developing effective therapies is so difficult," adds Galun. "Even if we can treat a few cancer cells, others will be resistant, and overcome any treatment we give." To address this, Galun focused on specific genetic elements called microRNAs.

Imagine if microRNA could be expressed in liver cells, enter cells in surrounding tissue, and start to inhibit tumours.

"MicroRNAs are small sequences of RNA molecules that are made from our DNA," he explains. "What makes microRNAs interesting is that they regulate other genes – and some microRNAs, such as microRNA 122, are known to have tumour-suppressive properties."

Each microRNA can target many genes at the same time – in the case of microRNA 122, over 200 genes are targeted. This particular microRNA is expressed almost solely in liver cells, with every liver cell containing about 70 000 copies of this microRNA 122.

"What is interesting is that if numbers of microRNAs are increased, then they don't stay in the cells," adds Galun. "They are secreted by cells in vesicles called exosomes, which are about the size of a virus." Galun recognised that regulating the expression of this tumour-suppressing microRNA could be a viable way to treat cancer.

Gene therapy from within

To investigate this further, Galun and his team performed high-throughput screening to identify other tumour-suppressive microRNAs. Next, they searched for small molecules capable of elevating the level of these relevant microRNAs in tumour cells and tissues.

A key benefit of microRNA-based therapeutics is that the delivery system is embedded within the body. This could be hugely significant, as researchers interested in gene therapy have long struggled to develop inexpensive and non-invasive delivery methods.

Identifying tumour-suppressing microRNAs, and screening for compounds that increase microRNA expression, could be a highly efficient and effective method of discovering and developing new cancer therapies.

"Pancreatic cancer patients usually die from metastasis, mainly in the liver," notes Galun. "So imagine if microRNA could be expressed in liver cells, exported out of these cells because of its increased expression, then enter cells in surrounding tissue and start to inhibit tumours."

The RxmiRcanceR project also discovered that microRNA 122 was found to target a handful of enzymes responsible for the production of triglycerides – a type of fat – in the liver. This could lead to possible new treatments for liver conditions such as non-alcoholic steatohepatitis, now the most common cause of cirrhosis.

The project's findings are in the process of being published, and Galun expects that patents for effective compounds identified through this work will follow.

PROJECT
RxmiRcanceR – Tumor suppressive microRNAs for cancer therapy

COORDINATED BY
Hadassah Hebrew University Hospital of Jerusalem in Israel

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/786575

PROJECT WEBSITE
eithangalun.com

A new hope for treatment-resistant breast and ovarian cancer

The EU-funded TargetBRCA project has identified new ways to attack tumours that resist conventional treatments such as chemotherapy.

Over 2.5 million people worldwide were diagnosed with breast or ovarian cancer in 2020. Within these are cancers that are resistant to current forms of treatment, carrying a high rate of mortality.

"The emergence of cancers that are resistant to existing therapies highlights the urgent and unmet need for additional therapeutics," says Raphael Ceccaldi, a researcher at the Curie Institute.

With the support of the TargetBRCA project, Ceccaldi is leading an effort to develop new methods for treating aggressive forms of breast and ovarian cancers that can resist such treatments as chemotherapy.

Stopping tumours in their tracks

Ceccaldi's research, which received additional support from the ERC, focused on characterising new molecules with the potential for targeting and inhibiting a specific enzyme associated with the formation of aggressive tumours.

Our treatment is nothing short of a paradigm shift, the first step towards safe and effective therapies for chemo-resistant tumours.

"The main goal of our proof-of-concept project was to generate enough data to establish partnerships with pharmaceutical companies or private investors to develop a clinical-grade inhibitor for treating chemo-resistant breast and ovarian tumours," explains Ceccaldi.

This goal was achieved in August 2023, when the project entered into a research collaboration agreement with ArgoBio Studio, a private investor. Together, they have since launched a start-up dedicated to developing targeted therapies for breast and ovarian cancers.

Innovation linked to basic research

In addition to securing this important partnership, the project generated data about potential new tumour-blocking molecules. However, getting this data wasn't always easy.

For example, after several months of intense investigation on a potential molecule, researchers realised they were likely heading down a dead end. The project was paused while researchers conducted additional research on the biology of the DNA repair target.

Understanding this, they were then able to adapt their work on the potential tumour-blocking molecule accordingly. "It's important to always remember that innovation must be tightly linked to basic research," notes Ceccaldi. "You simply cannot innovate without first having the strong basic science to back you up."

Thanks to this flexibility, the project now has a portfolio of candidate molecules that are entering the 'hit-to-lead' phase. This is an important milestone on the route to becoming a preclinical grade molecule, and one that will be further accelerated by the new start-up's fundraising prowess.

A paradigm shift in cancer treatment

According to Ceccaldi, TargetBRCA represents a new hope in the race to cure aggressive breast and ovarian cancers. "Our treatment is nothing short of a paradigm shift, the first step towards the development of safe and effective therapies for treating chemo-resistant tumours," he concludes.

In addition to the work that will be carried out by the soon-to-be announced start-up, Ceccaldi has lodged an application with the European Innovation Council Transition Programme, where he hopes to be able to further advance the work started during the TargetBRCA project.

PROJECT
TargetBRCA – To develop a new targeted therapy for the treatment of naive and PARP inhibitor-resistant BRCA1/2-mutated tumors

COORDINATED BY
Curie Institute in France

FUNDED UNDER
Horizon Europe-ERC

CORDIS FACTSHEET
cordis.europa.eu/project/id/101059469

Delivering chemotherapy with a lighter touch

Researchers working on the EU-funded THERMONANO project have developed subcutaneous chemotherapy that could allow patients to administer treatment from the comfort of their own home.

Despite significant improvements in cancer diagnosis and treatment, cases are predicted to rise by around 70 % over the next two decades as a result of an ageing and growing population.

Cancer treatment is often based on intravenous (IV) chemotherapy, which usually requires hospitalisation and can be very uncomfortable for patients. One promising alternative is subcutaneous (SC) chemotherapy, where drugs are inserted just below the skin.

The THERMONANO project, which was funded by the ERC, developed new treatments based on drug-polymer conjugates, nanomedicines which can be delivered via a simple SC administration.

"We sought to develop a chemotherapy strategy that is more comfortable and less dangerous for the patient, and also less costly, to significantly decrease the financial burden on patients and healthcare systems," explains Julien Nicolas, French National Centre for Scientific Research (CNRS) research director at the Galien Paris-Saclay Institute in France and THERMONANO project coordinator.

Building sophisticated nanocarriers

While SC injectables are more comfortable for patients and allow them to self-administer at home, most of the anticancer nanocarriers currently developed are not suitable for SC administration, as early release of the anticancer drugs causes local toxicity at the injection site.

Sophisticated nanocarriers are difficult and expensive to build, and, despite encouraging results, there are only a few examples of successful treatments.

The THERMONANO team developed a scalable approach for the SC administration of anticancer drugs. The drug delivery system is made of one anticancer drug molecule attached at the extremity of a well-defined, water-soluble biocompatible polymer chain.

We sought to develop a chemotherapy strategy that is more comfortable and less dangerous for the patient, and also less costly.

Nicolas has been working on the design, synthesis and evaluation of polymeric prodrugs for the last 10 years, in particular on the approach of growing the polymer from the drug in a controlled manner.

This approach – the 'drug-initiated' method – is flexible, easy to perform, requires only a few synthetic steps and gives high yields. "During this project, we have applied this approach to the synthesis of water-soluble polymer prodrugs and carried out their comprehensive preclinical evaluation," adds Nicolas.

Through the project, the new polymer prodrugs were evaluated for several properties, including their SC injectability, drug release abilities, toxicity on two different cancer cell lines, and anticancer efficacy.

"We demonstrated that our polymer prodrugs could be safely injected subcutaneously without inducing local toxicity, while outperforming a commercial competitor version for IV administration. This opens the door to the safe transposition from IV to SC chemotherapy," says Nicolas.

Founding a start-up

Owing to the promising results achieved during the project, the THERMONANO team, along with several colleagues, founded the start-up Imescia to advance the technology.

The enterprise aims to find industrial partners who could use the technology to administer drug molecules in SC, and to bring a first treatment into clinical trials as early as 2024. Imescia is currently seeking funding.

"The overall idea is to apply this strategy to a very wide range of anticancer drugs (not just small molecules) and thus safely and effectively transpose IV chemotherapies to SC chemotherapies," says Nicolas. "We hope that this new administration platform will represent an important step towards simplified chemotherapy, enabling patients to be managed at home, or even to self-administer their treatments."

PROJECT
THERMONANO – Nanoassemblies for the subcutaneous self-administration of anticancer drugs

COORDINATED BY
National Centre for Scientific Research in France

FUNDED UNDER
Horizon 2020-ERC

CORDIS FACTSHEET
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Revealing global inequalities in female cancers

The EU-funded VENUSCANCER project is seeking to understand the reasons behind starkly different patterns of survival and avoidable deaths in cancers affecting women around the world.

Every year, around 2.5 million women are diagnosed with either breast, ovarian or cervical cancers. These cancers are responsible for around 900 000 deaths every year.

But the picture is far from uniform around the world. Major differences in treatment options and survival exist from country

to country, with patients in the developing world facing far higher mortality rates.

These patterns have been uncovered by CONCORD, a global surveillance programme to monitor trends in cancer survival, run by the Cancer Survival Group at the London School of Hygiene & Tropical Medicine (LSHTM) in the United Kingdom.

The VENUSCANCER project, which was funded by the ERC, is working to unpick the reasons underlying global inequalities in cancer care and survival, to better prevent avoidable deaths.

"We believe the first worldwide comparison of patterns of care for breast, cervical and ovarian cancers will help to explain the reasons for most of the persistent international inequalities in survival for these cancers in women," explains Claudia Allemani, professor of Global Public Health at LSHTM and VENUSCANCER principal investigator. "The results will offer guidelines to policymakers on future directions for cancer control strategies."

The results will offer guidelines to policymakers on future directions for cancer control strategies.

A global view of cancer mortality

The VENUSCANCER team is analysing existing data in the CONCORD database to estimate the number of avoidable deaths from each type of cancer. At the same time, participating cancer registries are submitting new high-resolution data including details about cancer diagnosis, treatment and socio-economic status.

VENUSCANCER provided financial support for 10 registries in low-income and middle-income countries to aid with data collection. "This investment has greatly increased the quantity and quality of the detailed data required," says Allemani.

Through three working group meetings, the project developed a study protocol and specification for data collection. This was finalised in November 2019, and the team issued a call for data the following month. Then the COVID-19 pandemic hit, causing huge and prolonged disruption to data collection, staffing, data submission and quality control. Field trips were impossible between 2020 and 2022.

Yet despite the delays, new data is arriving. By August 2023, the project had received 190 data sets from 70 cancer registries in 32 countries, including information on 126 505 women diagnosed between 2015 and 2018. Several further data sets are expected by mid October 2023.

"During an unprecedented pandemic, we consider it a major achievement to have completed the protocol for data collection after analysis of over 400 questionnaires, managed data collection, as well as designed and finalised several of the planned analyses," adds Allemani.

Promising early results

The team has carried out preliminary analyses on diagnoses and treatments, with striking results. Among 94 656 women diagnosed with breast cancer, the proportion of tumours classified as early stage ranged from 12 % in Romania to 50 % in the United States. Breast-conserving surgery and radiotherapy was offered to over 70 % of women with early breast cancer in Belgium and Norway, but to only 19 % in Thailand.

Node-positive tumours ranged from 22 % in the United States to 34 % in Ecuador and Romania; chemotherapy treatment was received by 28 % of women in Norway, ranging up to 88 % in Thailand. The team expects most results to be published by mid 2024.

"VENUSCANCER is still far from over," says Allemani. "I hope it will become a prototype for similar high-resolution studies to explain inequalities in survival from other cancers."

PROJECT
VENUSCANCER – Women's cancers: do variations in patterns of care explain the world-wide inequalities in survival and avoidable premature deaths?

COORDINATED BY
London School of Hygiene & Tropical Medicine Royal Charter in the United Kingdom

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