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European Commission

CORDIS Results Pack on

chemical biology

A thematic collection of innovative EU-funded research results

July 2020

A chemical toolbox as a response to biological questions

Research and Innovation

Contents

Editorial

In medieval times, alchemy was the forerunner of chemistry, and was known as the 'handmaid of medicine'. Ironically, now that the boundaries between scientific disciplines are becoming less distinct, this relationship is much stronger. This CORDIS Results Pack illustrates how chemical biology provides tools , to understand the epidemiology of a variety of diseases, and to design more efficacious drugs.

The human body is a sophisticated chemical machine – precise and efficient. Normal function and disease are closely intertwined with the coordination of hundreds of intricate chemical reactions. Interdisciplinary cooperation is essential to obtain clear insight of how the body works and to decipher the chemical links between physiological and pathological conditions. Combining the core tenets of both disciplines, chemical biology reveals important molecular structures, methods and tools to manipulate and study biological processes at the chemical level. Studies often go hand in hand with other crossover fields of chemistry: synthetic chemistry, analytical chemistry and physical chemistry.

The EU's contribution to health

The European Commission fully supports research and development in health technologies. In its Seventh Framework Programme (FP7), it allocated more than EUR 6 billion for research projects with focus on three key areas: 'Biotechnology, generic tools and medical technologies for human health', 'Translating research into human health' and 'Optimising the delivery of healthcare to European citizens'. In total, 552 projects received funding between 2009 and 2013.

During the Horizon 2020 programme (2014–2020), the EU invested more than EUR 7 billion in the societal challenge 'Health, demographic change and wellbeing' focusing on translational collaborative health research. In total, 562 projects related to chemical biology received funding.

From 2009 to 2018, around 7 % of EU projects related to chemical biology and were funded by the European Research Council (ERC).

Highlighting groundbreaking EU projects

This CORDIS Results Pack features eight projects plus a short introduction to an ongoing but very promising initiative in its first research stages. The projects pioneered the design of chemical tools that enable better understanding of a variety of diseases, including cancer, infectious diseases and neurodegenerative disorders. Developments also have far-reaching implications for drug discovery and delivery. All projects are funded by the ERC.

The ongoing aLzINK project has identified an important drug target that could prevent the cascade of events that, over time, ends in Alzheimer's disease. Targeting more effective drug delivery, the BTVI project used 'prodrugs' that reveal their therapeutic action once they are converted within the body into a pharmacologically active drug. The project demonstrated synthesis of cancer drugs, vasodilators (drugs used to treat cardiovascular conditions) and antibacterial drugs delivered to the target tissues or organs.

With the aid of imaging techniques, in particular fluorescent tracers, AUTO NERVE project's outcomes help preserve the fine network of nerves surrounding a prostate tumour, making them more visible and, as a consequence, operations less invasive. In INCYPRO, researchers developed a new chemical stabilisation strategy to make enzymes more durable and alter their activity to ultimately produce more efficient drugs. Another project, LEGO, produced synthetic molecular constructs built like Lego bricks that redirect the body's own immune defence – its antibodies – to go after cancer cells.

The MINIRES project created an elastic material that mimics biological tissues for use in facial injection fillers and biomedicine. The design approach involved modification of a natural protein (resilin) with rubber-like properties. Meanwhile, the NICHOID project produced synthetic cell cultures to study what controls the fate of stem cell differentiation. Results can prompt tissue repair and regenerative medicine. In a similar vein, REGENERBONE developed biomimetic films with bone-regenerating properties that cause less adverse effects than grafts taken from the patient's own body.

Finally, the ongoing VERDI project is developing specialised nanoparticles to fight bone diseases like cancer, infections and osteoporosis.

Copper is the metal culprit in Alzheimer's disease

More than a century ago, German psychiatrist Alois Alzheimer noted distinctive plaques and neurofibrillary tangles in the brain tissue of the patient he treated before her death at 55. EU scientists have identified a drug target that could prevent the cascade of events that, over time, ends in Alzheimer's dementia.

Alzheimer's disease (AD) was first officially described in 1906 and the classification 'Alzheimer's disease' was included in a psychiatry textbook a few years later. Despite more than a hundred years of clinical data and research since then, many questions remain. The aLzINK project, funded by the EU's European Research Council (ERC), has answered an important one, pointing the way to an important target for drug candidates that could prevent the development of this devastating degenerative neurological disease.

Not all metals are created equal

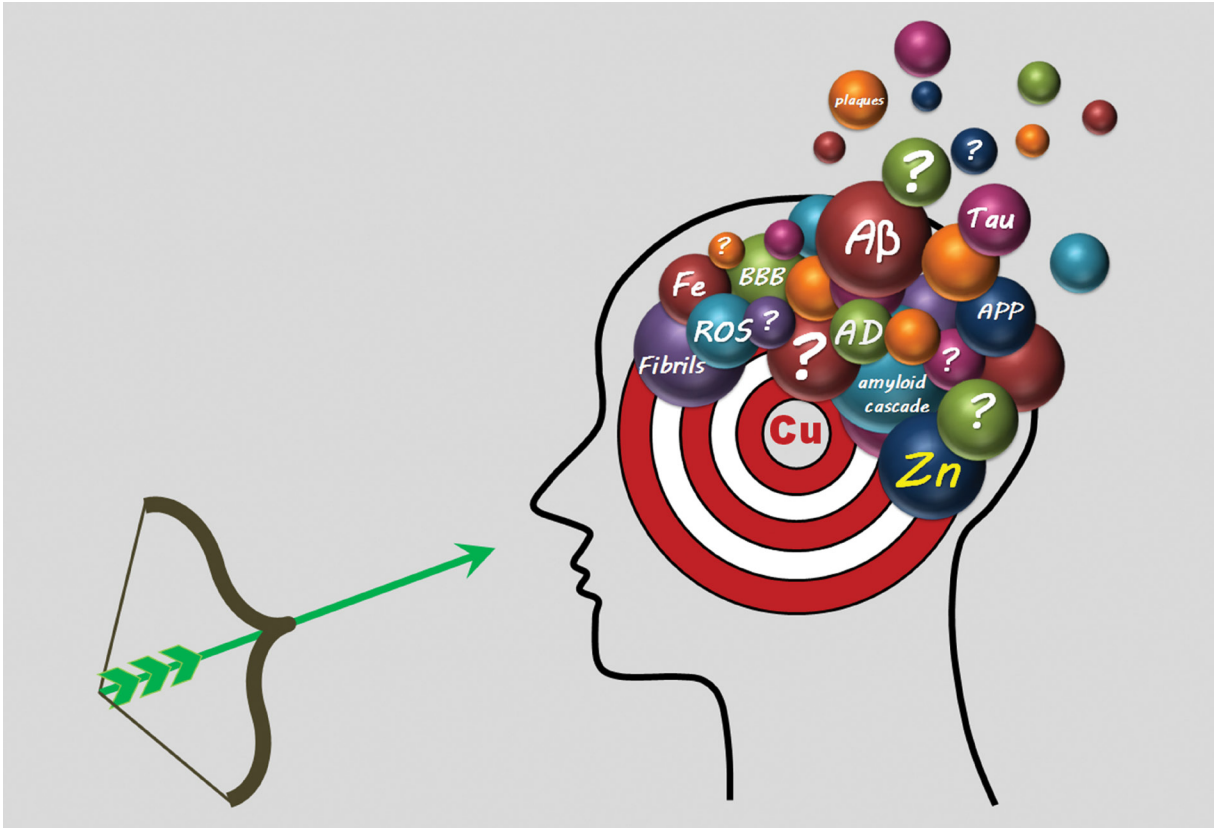
For the last 30 years, the amyloid cascade hypothesis has been a key focus of AD research. It proposes that the aggregation of amyloid-β (Aβ) peptides (where peptides are two or more amino acids linked in a chain) is an early and the first key event. The second is the formation of reactive oxygen species (ROS) related to oxidative stress. At the final stage, self-assembled peptides are gathered in so-called senile plaques, a hallmark of the disease.

Metal homeostasis (maintaining the appropriate metal balance required for physiological functioning), particularly of copper (Cu) and zinc (Zn), has been linked to all three steps. ERC grantee Christelle Hureau-Sabater explains: "Cu can be found in two oxidation states, Cu+ and Cu2+. While Cu can trigger ROS formation Zn is inert and cannot. Both ions can link to Aβ peptides, but in different ways, thus modulating Aβ peptide aggregation differently. One therapeutic strategy relies on removing metal ions bound to Aβ peptides. We hypothesised that Cu should be selectively removed, which makes the design of therapeutic molecules/drug candidates (called ligands or chelators) more difficult." The aLzINK project set out to develop guidelines to do so.

Many therapeutic approaches to AD have failed, including those targeting metal ions. In aLzINK, we have demonstrated that many criteria must be considered, and we have elucidated important features regarding those criteria.

Overcoming challenges, hitting the therapeutic 'bull's eye'

The Aβ peptide is a short, intrinsically disordered protein of about 40 amino acids that is derived from a longer membrane protein. Its flexibility and lack of a preformed 3D structure make it difficult to identify where Cu and Zn bind to the peptide and how. According to Hureau-Sabater: "We overcame this issue by using many complementary techniques including sophisticated X-ray absorption spectroscopy or XAS." XAS is widely used to determine the local geometric and/or electronic structure of matter relying on synchrotron radiation for intense and tuneable X-ray beams.



© Christelle Hureau

Thanks to innovative protocols and collaboration with other groups, Hureau-Sabater's team overcame challenges, successfully meeting its original objectives. "We have precisely shown why AD drug candidates should specifically target Cu. We tested several molecules in solutions and some in cells with promising results." This provides a starting point for future studies of the therapeutic potential of Cu chelators (sequestering agents) and related compounds. Along the way, the researchers also highlighted the utility of inorganic prodrugs instead of the purely organic parent ligand and discovered the importance of exchange rates between the ligands Aβ, Cu and Zn and of targeting the Cu+ state of copper.

Hureau-Sabater concludes: "Many therapeutic approaches to AD have failed, including those targeting metal ions. In aLzINK, we have demonstrated that many criteria must be considered, and we have elucidated important features regarding those criteria." aLzINK has opened a new door on more precisely targeted therapies for AD that could enhance benefits while minimising unnecessary side effects.

PROJECT
Alzheimer's disease and Zinc: the missing link?

COORDINATED BY
National Centre for Scientific Research in France

FUNDED UNDER
H2020

CORDIS FACTSHEET
cordis.europa.eu/project/id/638712

Cunning prodrugs maximise therapeutic benefit

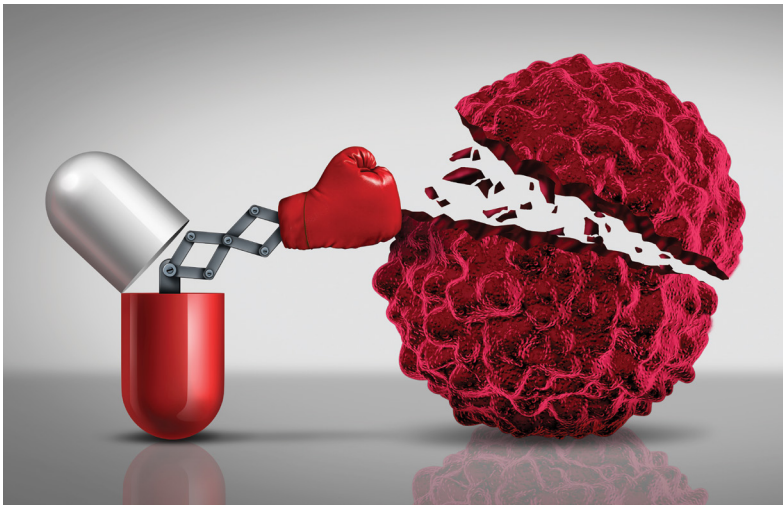
Despite advances in medicinal chemistry that make it possible to synthesise a plethora of drugs, their biodistribution and efficacy is far from optimal. To overcome this problem, European researchers have developed an innovative prodrug therapy where the active drug is synthesised at the site of action.

Absorption, distribution, metabolism and excretion are the main barriers that drugs must overcome to be effective. Reducing systemic exposure while maximising localised concentration at the site of interest is key for therapeutic benefit. Over the years, researchers have come up with various technologies to achieve localised drug delivery or synthesis using biologically inert prodrugs that are activated on site, usually with the help of enzymes. This approach is known as enzyme prodrug therapy (EPT), has potential application in cancer therapy for the delivery of cytotoxic agents.

Localised drug synthesis

Inspired by nature, scientists funded by the EU's European Research Council (ERC) proposed the use of native enzymes to achieve drug synthesis at the site of drug action, at the time needed and at the required concentration. In the process, they realised the importance of the chemical nature and biocompatibility of the right building blocks or precursor molecules for localised bioconversion by enzymes. They therefore invested time in developing innovative prodrugs rather than using commercially available ones.

For anti-tumour therapy, efforts focused on the bioconversion of prodrugs in the tumour microenvironment, as a safe, effective measure to suppress cancer cell growth. Prodrugs were engineered to localise in the tumour and exploit the unique cancer enzymatic fingerprint to undergo bioconversion into a highly potent anti-cancer drug.



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Apart from anti-cancer drugs, the BTVI project team worked towards antibacterial therapeutics to prevent bacterial colonisation of implants. Researchers developed enzyme-containing fibrous mats and surface coatings with catalytic activity that can be used on the surface of metallic implants already in medical use. To this end, they designed innovative prodrugs that reach the implant surface and get converted into antibacterial drugs.

Furthermore, the team discovered that inorganic nanoparticles exhibit catalytic activity mimicking human glycosidases and can be used for prodrug conversion. After deciphering the mechanism of catalysis, scientists developed nanozymes with diverse applications in biotechnology.

Advantages of EPT

Localised drug synthesis is an incredible opportunity and can rely on implanted enzymes, on the inherent catalytic property of the implant, or on the enzymatic repertoire of the disease.

"Localised drug synthesis is an incredible opportunity and can rely on implanted enzymes, on the inherent catalytic property of the implant, or on the enzymatic repertoire of the disease," explains ERC grantee Alexander Zelikin. Indeed, prodrugs present an amazing tool for medicinal chemistry as they inherently mask the toxicity of even the most powerful therapeutics. The capacity of natural enzymes to convert a wide range of substrates can be harnessed to synthesise multiple drugs, mediating combination therapy.

The delivered therapeutics don't necessarily have to be drugs but short-lived molecules, such as nitric oxide, with a broad spectrum of physiological activities. Nitric oxide has been characterised as the guardian of cardiovascular grafts because of its vasodilation properties and its ability to counteract platelet aggregation. Therefore, implementing EPT in vascular implants to achieve localised nitric oxide production is highly desirable.

"With the hard work of our interdisciplinary team we overcame scientific challenges and made significant progress in the field of medicinal chemistry," outlines Zelikin. Through implantable biomaterials or by harnessing the diseased tissue itself, the BTVI project has successfully delivered a novel methodology for localised drug synthesis expected to be embraced by the broader biomedical community.

PROJECT
First Biodegradable Biocatalytic VascularTherapeutic Implants

COORDINATED BY
Aarhus University in Denmark

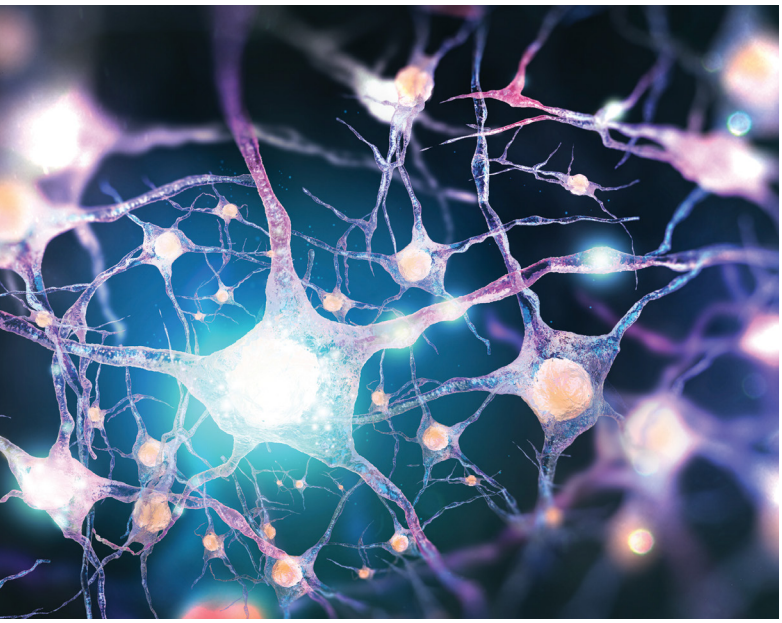
FUNDED UNDER
H2020

CORDIS FACTSHEET
cordis.europa.eu/project/id/617336

The (fluorescent) future of prostate cancer surgery

How can surgeons preserve the fine network of nerves surrounding prostate tumour that is invisible to the eye? Using fluorescent tracers to illuminate nerves, it may not be too long before surgical fields look more like Gray's Anatomy pictures.

Prostate cancer is the second most common cancer type in men worldwide, but it is highly treatable in the early stages. It begins in the prostate gland, which is just located below the bladder. Surgeons often rely on complete gland removal to resect the primary cancer. What's more, these operations often cause injury to peripheral nerves, which can result in urinary incontinence and erectile dysfunction. These two common side effects can be especially burdensome for patients and loved ones.



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Inner glow gives a sense of peripheral nerves

Funded by the European Research Council, the AUTO NERVE project offers the possibility of realising nerve-sparing prostate surgery through the use of imaging techniques, in particular fluorescent tracers. "Fluorescent tracers that specifically stain nerves allow surgeons to save the delicate anatomies surrounding the prostate," notes principal investigator Fijs van Leeuwen.

Project scientists used tracers consisting of peptides joined with fluorescent dyes that bind to peripheral nerves. When the tracer is excited by light of a particular wavelength, it emits a specific type of fluorescent light that can be detected by a dedicated camera system and visualised in real time during surgery. This imaging technique helps to making peripheral nerves glow in the surgical view and as such enables surgeons to clearly distinguish the boundaries between the tumour, healthy tissue and nerves.

The AUTO NERVE team identified a number of peptides that specifically bind to peripheral nerves. The most promising ones in terms of specificity and biodistribution (method of tracking where peptides travel) were tested during robotic surgery performed in large animals. Together with a market leader in the area of contrast agents, the project is exploring valorisation of the new tracers.

A non-invasive imaging technique without alternative

Currently, there are no alternative fluorescence imaging techniques that can visualise nerves during surgery. Certain ones that are tested in animal models involve the use of small molecules that emit weak fluorescent light in the ultraviolet. Another downside is that they migrate across the blood-brain barrier, meaning they accumulate in the central nervous system (CNS) and could induce systemic toxicity.

The fluorescent tracers developed in this project are labelled with conventional dyes such as fluorescein, cyanine-5 or cyanine-7 and bind specifically to nerves without crossing the blood-brain barrier that protects the CNS. "Practically, this means that we can now use clinical-grade camera systems and reduce the chance that a patient who undergoes a nerve-sparing prostate cancer surgery ends up with debilitating toxic side effects in the CNS," explains van Leeuwen.

Imaging autonomic versus somatic nerves

Fluorescent tracers that specifically stain nerves allow surgeons to save the delicate anatomies that surround the prostate.

The main difference between the autonomic and the somatic nerves in the peripheral nervous system is functional. The first controls internal organs and glands, while the second controls muscles and movement. AUTO NERVE benefited directly from the outcomes of its predecessor ILLUMINATING NERVES project – which involved the design of lead compounds suitable for imaging both types of nerves. Optimising the structure-activity relation of the lead compound as pursued within another proof-of-concept grant researchers received earlier, MY NERVE, and AUTO NERVE will increase the chances of its wide use in medicine.

Fluorescent tracers could make nerves glow in the dark so that operators become aware of their location in the surgical field. However, successful treatment of prostate cancer without complications is a relay race between oncological outcome (requires accurate tumour removal) and side effects (requires nerve sparing).

PROJECT
Tracers for targeting nerves in the autonomic nervous system

COORDINATED BY
Leiden University Medical Center in the Netherlands

FUNDED UNDER
H2020

CORDIS FACTSHEET
cordis.europa.eu/project/id/790079

New tailored approach signals a breakthrough in directed evolution of stable enzymes

Evolved by nature, enzymes are renewable and non-toxic, providing a green route to chemical synthesis and biotechnology, but sometimes the most useful ones need a helping hand to boost their activity and stability. EU-funded researchers devised an entirely new stabilisation strategy to make enzymes more durable and alter their activity.

Enzymes found in nature could be tweaked to perform new tricks by altering their DNA sequence. The glimmering of this idea, which earned an American chemical engineer the 2018 Nobel Prize in Chemistry, came from Darwin's conception of biological evolution that combines the processes of genetic mutation and recombination, and natural selection.

This evolutionary process is now increasingly being employed in chemical laboratories to create new enzymes: The process begins with finding an amenable enzyme that weakly performs the desired reaction that is then mutated and tested for the desired activity. After many optimisation cycles, an evolved enzyme with the desired activity wins out. This artificial, speeded-up version of the evolution process is called 'directed evolution'.

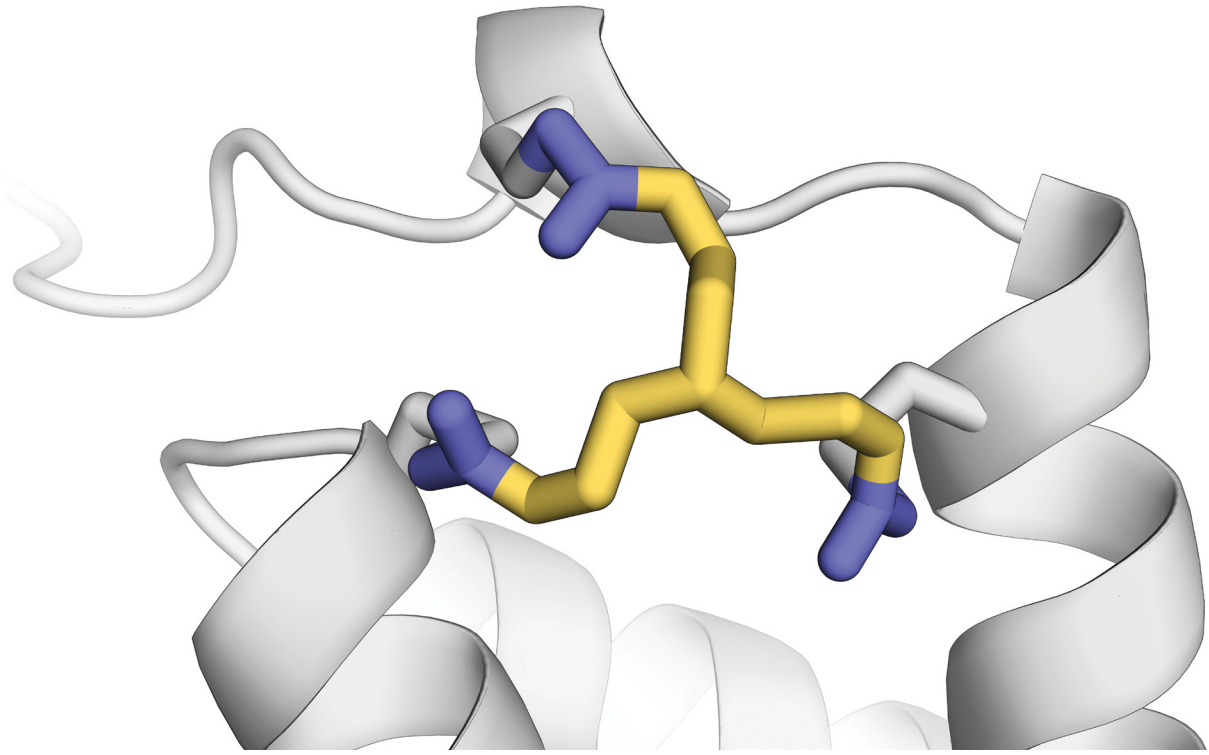
Enzymes developed using directed evolution are a green alternative to toxic metals or large amounts of organic solvents. Despite progress in the field, the use of enzymes for producing fine chemicals, materials and drugs is not fully harnessed due to their limited tolerance to non-physiological conditions. The elevated temperatures or unnatural microenvironments (such as extreme pH and the presence of organic solvents and detergents) often prove unsuitable to the enzymes, compromising their stability and thus their selectivity and activity.

Circular proteins are more stable

European scientists tackled the topic with support of the European Research Council (ERC). Professor of chemistry at the Department of Chemistry and Pharmaceutical Sciences at the VU Amsterdam Tom Grossmann and his team have synthesised and tested cross-linking reagents with diverse physical and chemical properties that bind to different parts of the enzymes to produce rugged and more efficient versions.

At the core of their work is an entirely new stabilisation strategy called 'in situ cyclisation of proteins' (INCYPRO). Grossmann explains the principle behind the concept: "INCYPRO enables a straightforward, computational and non-iterative design process that involves the introduction of three cysteines into the enzyme, which then react with an electrophile cross-linker with three centres."

The project team created different cross-linkers by 'decorating' a symmetric core structure – triethylamine, triazinane or benzene – with three electrophiles – acrylamide, chloroacetamide and vinyl sulphonamide (chemical species which attract electrons).



©Tom Grossmann

The cross-linker reacts with the three thiol side chains of the cysteines on the enzyme, resulting in a multicyclic protein that has a more robust (stable) core structure. The more 'electron-loving' the electrophile, the faster the cross-linker bonded to the thiol groups.

A better alternative to existing stabilisation approaches

INCYPRO utilises enzymes entirely composed of natural amino acids that can be obtained rapidly, cost efficiently and in large quantities. "Current enzyme stabilisation approaches require multiple optimisation cycles or involve non-natural amino acids which complicate enzyme production. This prolongs the design process and increases production costs of the new enzyme," adds Grossmann.

Straightforward and high-efficiency stabilisation approaches such as INCYPRO make a positive impact on the field of green chemistry.

What's more, an existing approach focuses on increasing the stability of a small part of a protein. Grossman and his team continued the work conducted by another EU-funded project, PEP-PRO-RNA, also supported by the ERC. "In PEP-PRO-RNA, we developed molecular architectures (cross-linkers) to connect two or three different parts of a protein fragment. We then devised INCYPRO to demonstrate that these types of cross-linkers can also stabilise the entire protein," notes Grossmann.

Robust and efficient enzymes are viable alternatives to toxic reagents used in the chemical and pharmaceutical industries, and often shorten the multi-step chemical/drug synthesis routes. "Straightforward and high-efficiency stabilisation approaches such as INCYPRO make a positive impact on the field of green chemistry," concludes Grossmann.

PROJECT
A Technology for the Generation of Stable Enzymes

COORDINATED BY
Stichting VU in the Netherlands

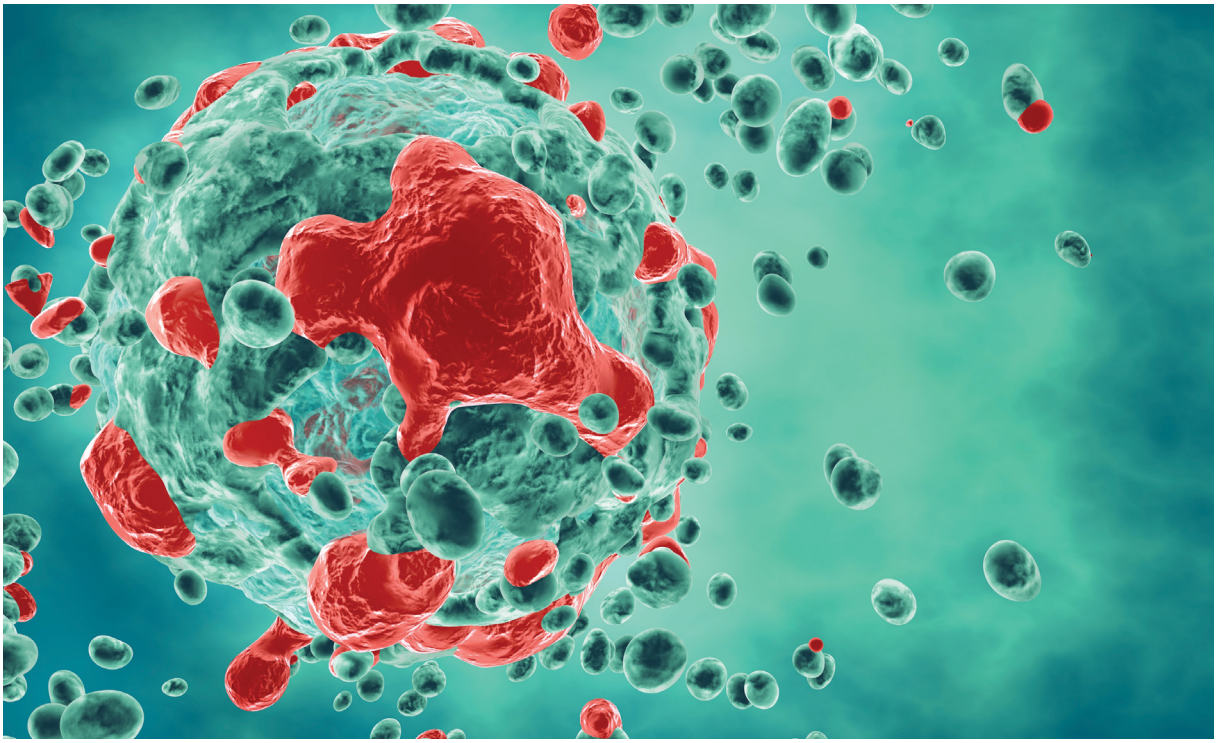
FUNDED UNDER
H2020

CORDIS FACTSHEET
cordis.europa.eu/project/id/839088

Antibody-recruiting sugar-based molecules: The 'sweet' approach to targeted cancer therapy

EU-funded scientists have produced synthetic sugar-based molecular constructs built like Lego bricks that lure in endogenous antibodies to specific surface proteins to destroy cancer cells. These bifunctional molecules could have a dramatic impact on cancer treatment and ultimately become a backbone of cancer therapy.

At its best, the immune system is the ideal weapon against infectious diseases, as it eliminates viruses or bacteria that invade the body, killing infected cells while leaving healthy tissue intact. The specificity and power of the immune system as a way to attack cancer cells more strongly and effectively has not been overlooked by cancer scientists.



Therapeutic monoclonal antibodies are amongst the most prominent passive immunotherapies that have revolutionised targeted cancer therapy. They target and bind to antigens – proteins that are mainly expressed on diseased cells – and employ different mechanisms to trigger death of cancer cells. Despite their success, monoclonal antibodies have significant limitations.

"Fully synthetic supramolecular structures composed of diverse functional units that bind simultaneously to the cancer cell surface and to natural antibodies offer an excellent alternative to classical immunotherapy that utilises monoclonal antibodies. They can recognise different biomarkers that account for tumour heterogeneity which rapidly evolves during the disease," explains Olivier Renaudet, Principal Investigator of the ERC project LEGO. Realising diverse combinations of both antibody and tumour-binding molecules offers a higher probability of recognising a larger population of a patient's cancer cells.

A Lego-like molecular approach to manipulate the immune system

The project pioneered the synthesis of synthetic biomolecular structures called antibody-recruiting glycodendrimers (ARGs) that consist of optimal combinations of antibody- and tumour-binding modules. "Our 'Lego-like' approach allows the easy preparation of synthetic molecules to redirect the body's own immune defence – endogenous antibodies present in the human bloodstream – to go after disease-causing entities such as cancer cells," explains Renaudet.

Researchers merged different approaches such as supramolecular chemistry, molecular engineering, biochemistry, immunochemistry and organic chemistry to design complex chemical compounds of unprecedented molecular composition. These trigger potent cytotoxic effects against cancer cells upon formation of a ternary complex between antibodies, an ARG and cells. The antibody-binding module attaches to endogenous antibodies, while the tumour-binding module binds tightly to specific proteins expressed on the tumour cell surface. By creating this 'bridge', ARGs enable endogenous antibodies to coat tumour cells, leading to their destruction.

"We first identified potent antibody- and tumour-binding modules based on tests with different human sera (the fluid components of blood) and tumour cell lines, respectively. We then implemented a multi-click chemistry approach to combine these two functional moieties in the same supramolecular construct," explains Renaudet. By using innovative glycoarray (a microarray of glycodendrimers) technology, the team screened and identified multivalent structures (ligands) with optimal affinity and selectivity for diverse carbohydrate-binding proteins.

Our 'Lego-like' approach allows the easy preparation of synthetic molecules to redirect the body's own immune defence [...] to go after disease-causing entities such as cancer cells.

Project partners performed a successful proof of the principle of the idea. LEGO's first lead compound demonstrated the ability to form a ternary complex and induce up to 70 % immune-mediated cytotoxicity in vitro against the human melanoma cell line M21, without immunisation and using human serum as a unique source of immune effectors.

Expected impact

The ability to design and synthesise molecules that emulate the functionality of our immune system represents a great advancement in the field. The novel methodologies introduced by LEGO could open new avenues for targeted immunotherapy, giving hope for safe and effective treatment options using synthetic chemistry. A similar approach could also be used to treat infections by pathogens (bacterial and viral) for which limited treatments are available.

PROJECT
Multimodal glycoconjugates: a molecular Lego approach for antitumoral immunotherapy

COORDINATED BY
University of Grenoble in France

FUNDED UNDER
H2020

CORDIS FACTSHEET
cordis.europa.eu/project/id/647938

Elastic facial fillers inspired by jumping insects may be coming soon

Incredible elasticity enables fleas to jump and mosquitoes to beat their wings 600 times per second. An elastic polymer (elastomer) produced using only a small fragment of the natural protein, resilin, will make this elasticity available for numerous applications at competitive prices.

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Resilin is a natural rubber-like protein with outstanding elasticity critical to the flight and jumping systems of insects. It is normally disordered; in response to stress, it becomes organised – and elastic. Recently, scientists discovered that they can replicate this behaviour using just a small part of the original peptide. The EU-funded MINIRES project enabled them to pave the way to large-scale production of innovative bioelastomers for the plastics, biomedical, and personal care sectors at a fraction of the current cost.

Reducing the rubbery bounciness of insects to several amino acids

Halogens include fluorine, chlorine, bromine and iodine. Replacing a hydrogen with a halogen (halogenation) is a very important reaction in organic chemistry. Over the last decade, its role in the production of biogels has gained increasing attention. Project coordinator Pierangelo Metrangolo of the Politecnico di Milano explains: " We focused on a well-conserved repeating unit of seven amino acids in resilin. By strategically halogenating this unit with two bromines, we demonstrated the emergence of a viscoelastic behaviour that resembles that of the full protein and that is not observed in the naturally occurring peptide." This halogenation led to a more organised arrangement of the peptide, which then allowed it to form fibrils that resulted in a dense hydrogel. The gel, made of the heptapeptide, exhibited viscoelastic and self-healing properties resembling those of the full resilin protein.

Reducing the cost and complexity of production

Metrangolo continues: "Commercially available elastomers are currently large, complex polymers whose elasticity depends on covalent bonding between subunits, usually introduced

by chemical or light-induced chemical reactions. In our very short peptide, we rely on physical cross-links created exploiting halogen atoms as 'sticky' sites. This simple molecular structure is easy and inexpensive to produce." Scientists scaled-up the synthesis of the peptide from the lab scale to the 10-gram scale at a cost predicted to be 100-fold lower than that of the full protein production.

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A world of opportunity

MINIRES resulted in a patent for the technology. The team has identified three important market opportunities: facial injection fillers and haircare products, thermoplastic elastomers, and biomedicine. The organic personal care and cosmetic products segment is expected to reach USD 19.8 billion by 2022, of which skincare products represent more than 30 % followed by haircare. The serendipitous discovery that the brominated peptide prevents UVA damage enhances attractiveness for skincare. The superior properties and low cost of MINIRES gels could place the group as a global leader in the huge thermoplastic polymer market. Finally, MINIRES peptides could find use in medical devices and bioscaffolds.

MINIRES may have finished but innovation and discovery are flourishing. "During the course of the project, we also discovered that our brominated peptide can be successfully combind with other biomacromolecules. New hybrid materials with improved performance and tailored properties will be a focus of future research," says Metrangolo. The team recently won the 2017 Switch2Product innovation challenge that provides support to bring innovative ideas to market, and now Metrangolo is revving up to deliver novel bio-inspired macromolecules with finely tuned properties for targeted applications.

PROJECT
A Minimalist Peptide Elastomer

COORDINATED BY
Politecnico di Milano in Italy

FUNDED UNDER
H2020

CORDIS FACTSHEET
cordis.europa.eu/project/id/789815

A novel microengineered stem cell niche

We will soon be able to cure a disease not with pills but through stem cell therapies. Understanding and controlling stem cell differentiation is of great importance and requires innovative tools such as the synthetic niche, or substrate, developed during the NICHOID project.

Regenerative medicine aims to repair and recover the biological function of damaged tissues and organs often using stem cells, for example in cartilage repair or wound healing. However, this requires the development of culture substrates that mimic the native environment of stem cells and can support their expansion and differentiation.

Polymerisation of an innovative stem cell substrate

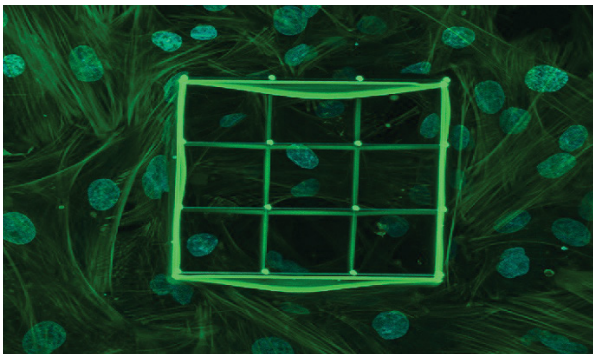
Polymeric scaffolds are structures engineered from synthetic polymer materials such as poly-L-lactic acid or poly-glycolic acid. They are emerging as synthetic 3D environments capable of influencing cell growth and proliferation, together with feeder layers or other biological compounds that are employed to maintain the phenotype of stem cells. To overcome safety concerns associated with the use of such additives and feeder layers, the NICHOID project, funded by the EU's European Research Council (ERC), developed a polymeric scaffold with grid architecture using a microfabrication technology called two-photon laser polymerisation. "Our approach led to the development of the user-friendly and safe Nichoid substrate," explains principal investigator Manuela Teresa Raimondi from the Polytechnic University of Milan in Italy.

The Nichoid essentially prevents stem cell spreading during proliferation by mechanically confining cells in the grid, thus avoiding this master switch towards differentiation.

Nichoid was tested on mesenchymal stem cells (MSCs) known for their regenerative capacity in orthopaedic, plastic and reconstructive surgery applications, as well as for their immune-suppressive potential in organ transplantation. They are also sensitive to mechanical stimuli from the micro-environment. Mechanical cues transduced within cells are believed to determine cell fate as they alter nuclear shape and hence the import and export of transcription factors that are paramount for regulation of gene expression.

"The Nichoid essentially prevents stem cell spreading during proliferation by mechanically confining cells in the grid, thus avoiding this master switch towards differentiation," emphasises Raimondi. With the help of colleagues at the affiliate Polytechnic University of Milan and at the National Research Council of Italy, researchers observed a roundish nuclear configuration in MSCs adhered to the Nichoid microscopic grid, while a spread configuration was seen in cells attached to the flat substrate surrounding the grid. The latter morphology coincided with an increase in nuclear permeability and in the flow of signalling molecules that induce cell differentiation.

The observation that in stem cells nuclear import of transcription factors activating cell differentiation is regulated primarily by nuclear membrane strains was also supported through computational prediction of nuclear import flow as a function of cell morphology. This geometric control of cell stemness opens an avenue towards reprogramming the capacity of stem cells to generate multiple (multipotency) or even all cell types (pluripotency) in culture, without the need of chemical agents or genetic modifications.



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Future prospects of the Nichoid substrate

The results obtained from the NICHOID project represent a substantial core of new basic knowledge on how to engineer stem cell function in culture. "The ERC was so visionary to fund me two additional proof-of-concept projects, during the NICHOID project, to boost the technology transfer of all my inventions," emphasises Raimondi. The proof-of-concept ERC-funded MOAB project will allow the researchers to integrate their Nichoid innovation into an existing miniaturised, optically accessible bioreactor. The aim is to exploit the Nichoid substrate in a drug discovery platform for testing drugs on 3D tissue-equivalents and organoids. Commercialisation of the device, developed thanks to the ERC funding, will take place by the Polytechnic University of Milan spin-off company MOAB Srl.

In light of the COVID-19 pandemic, Raimondi plans to promote the Nichoid substrate for the expansion of MSCs to cure COVID-19, based on a new therapeutic strategy already in clinical trial in China and in the United States. Moreover, she will use all the advanced research tools developed during the NICHOID project to speed up the preclinical testing necessary to bring new antiviral therapies and vaccines to the clinics.

PROJECT
Mechanobiology of nuclear import of transcription factors modeled within a bioengineered stem cell niche

COORDINATED BY
Polytechnic University of Milan in Italy

FUNDED UNDER
H2020

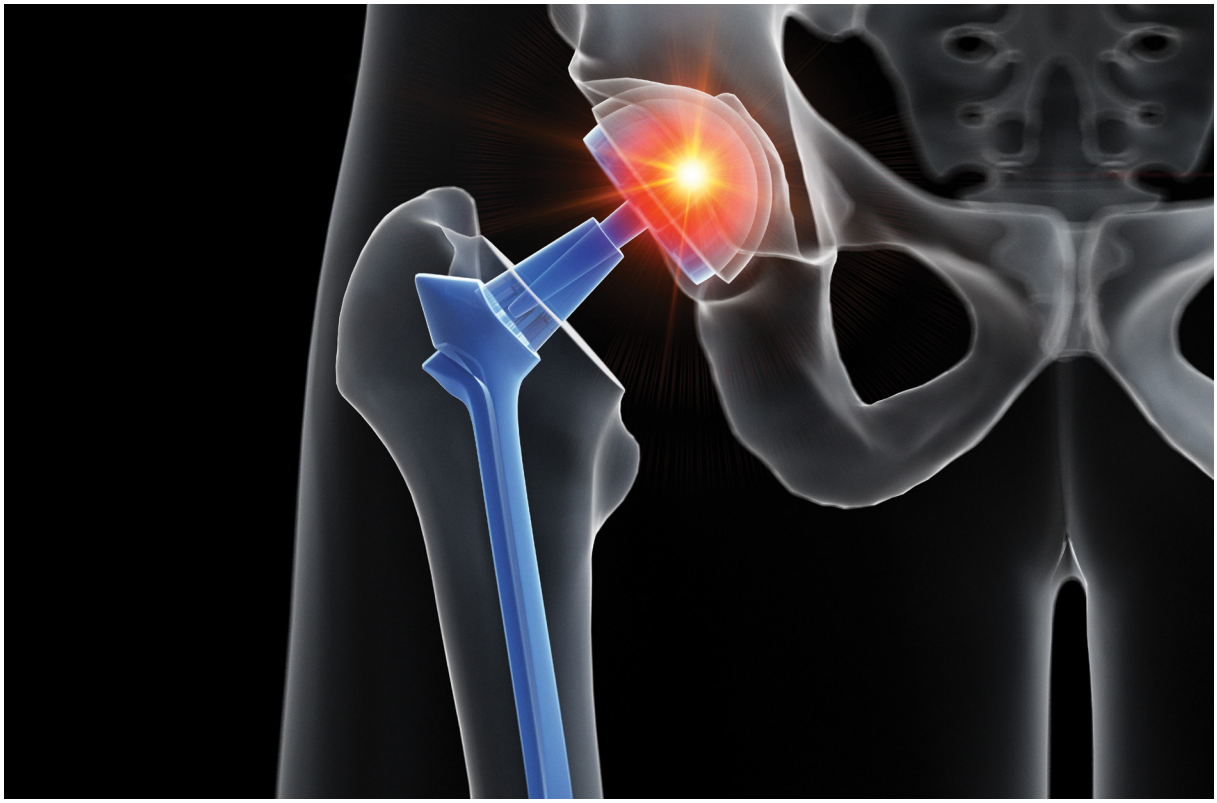
CORDIS FACTSHEET
cordis.europa.eu/project/id/646990

PROJECT WEBSITE
nichoid.polimi.it/

A versatile biomimetic film for coating bone implants

Currently, the gold standard for repairing critical-size bone defects that will not heal by themselves is to use the patient's own tissue (autograft). Since this process is associated with prolonged pain and high infection risks, European scientists have developed a biomimetic solution that can be adapted to individual patient needs.

In the field of orthopaedics and maxillofacial surgery, synthetic bone grafts have emerged as an alternative solution in hip replacement, face or jaw reconstructive surgeries and following curettage of tumours. Apart from mechanical properties, synthetic grafts nowadays demonstrate an osteoconductive capacity: molecules such as growth factors are incorporated in their design to trigger the bone regeneration after surgery. However, the grafts cannot control the delivery of these bioactive molecules, causing inflammation, infection, abnormal bone healing or are structurally insufficient to correct large-size defects.



A biomimetic film with bone-regenerating properties

Ideally, synthetic grafts should be designed to mimic the bone environment in vivo, allowing the spatial and temporal release of bioactive molecules at physiological doses. To address this, the EU-funded REGENERBONE project worked towards innovative medical implants with osteoinductive properties. The project built on technology developed during the EU-funded BIOMIM project consisting of biomimetic films that can be deposited on any material.

Built using a layer-by-layer assembly technique, the biomimetic films contain two biopolymers that are widely present in cartilage and bone tissues: hyaluronic acid and a polymer of lysine. In addition, they contain the bone morphogenetic protein 2 (BMP-2) responsible for the activation of bone progenitor cells and their differentiation into bone cells. BMP-2 has already received approval for bone repair in the clinic. "By controlling the conditions for BMP-2 loading in the films, we can precisely control the dose of BMP-2 that we will deliver in vivo," emphasises principal investigator Catherine Picart.

This is a great advantage, as it renders our films suitable for all types of synthetic grafts currently used in bone replacement strategies.

Moreover, the biomimetic films have a nanoscale porosity that endows them with controlled stiffness and enables to fine-tune the release of BMP-2 close to the implant surface.

The biomimetic films can be deposited onto practically any implantable material irrespective of chemical composition, geometry, shape and size including ceramics, polymers and metals. "This is a great advantage, as it renders our films suitable for all types of synthetic grafts currently used in bone replacement strategies," highlights Picart.

Bone-regeneration efficacy

Film-coated implants demonstrated an osteoinductive capacity in vivo when tested in preclinical models. Moreover, scientists used hollow polymeric cylinders coated with the osteoinductive films to repair a bone defect of critical size in rat femurs. The extent of the repair was dependent on the BMP-2 dose and the newly formed tissue resembled the physiology of native bone.

REGENERBONE scientists were also able to repair mandibular defects in a large animal model. This type of defect resembles in size those that surgeons have to repair in the clinic. For this purpose, they engineered an innovative implant to fill the bone defect. Coating with the biomimetic film delivered efficient bone repair in a BMP-2–dependent manner without adverse effects.

Future directions

Overall, the promising results have urged REGENERBONE scientists to obtain regulatory approval for testing the biomimetic products in human trials. This will take place in collaboration with the Clinical Investigation Centre for Innovation Technology Network CIC-IT in Bordeaux, specialised in the translation of innovative medical devices. Importantly, the versatility of the technology will enable the construction of tailored implants adapted to the needs of each particular bone defect.

The use of biomimetic films extends beyond bone implants and can be employed to coat cell culture microplates for studying cellular signalling and controlling stem cell differentiation. This application was explored under the BIOACTIVECOATINGS project, funded by the EU's European Research Council, and can be used for drug screening, tissue engineering and toxicology purposes.

PROJECT
REGENERATING LARGE BONE DEFECTS

COORDINATED BY
The Grenoble Institute of Technology in France

FUNDED UNDER
H2020

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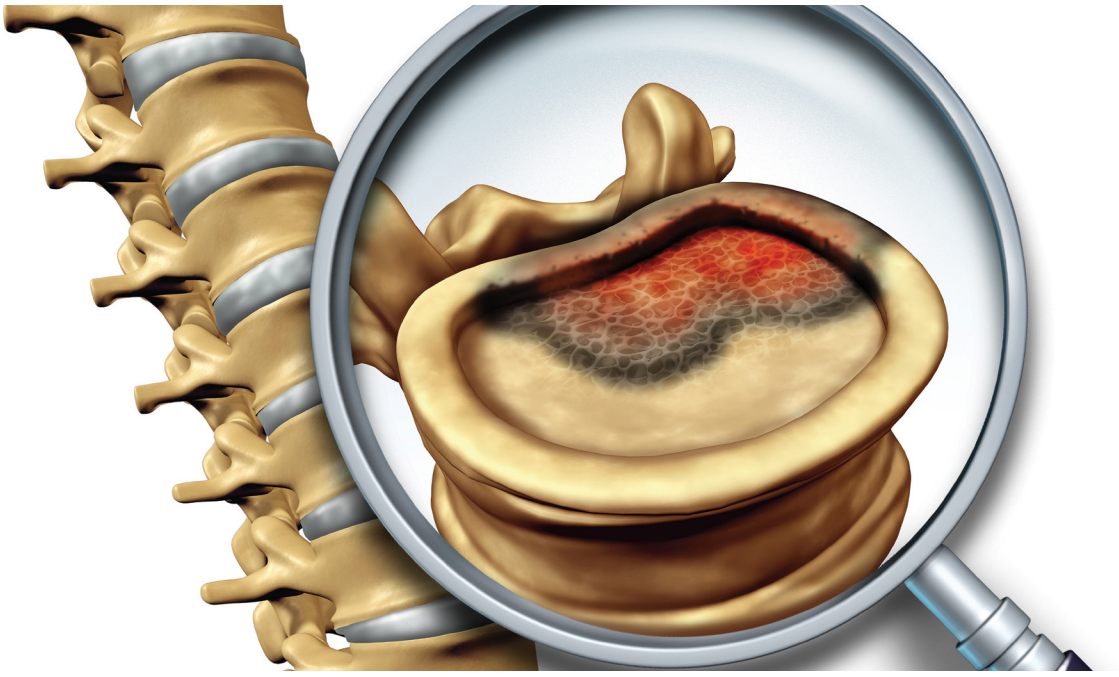
cordis.europa.eu/project/id/790435

Tiny silica particles: Powerful agents that could wipe out bone diseases

EU-funded scientists successfully created silica nanoparticles that can revolutionise treatments for complex bone diseases. These tiny particles can trap in their pores biomolecules to fight osteoporosis, antibiotics to combat bone infections or life-saving toxins to attack bone cancer.



Nanoparticles constitute the main pillar in nanomedicine: They are now continuously being explored for their use in targeted drug delivery or repairing damaged tissues such as bones and muscles.

Inspired by this potential, scientists initiated the VERDI project funded by the EU Research Council (ERCEA). At the core of the project's vision was to create a library of active ingredients and targeting mechanisms according to the disease being treated.

This library could serve as the ideal starting point for designing customised nanoparticles depending on the bone pathology.

Using this multifunctional nanoplatform, scientists can equip 'secret powerful agents' – mesoporous silica nanoparticles – with sophisticated weapons to fight different but frequently associated bone diseases. These include cancerous tumours that grow inside bone tissues disguised as healthy cells, osteoporosis that weakens bone reconstruction, and bacteria that infect healthy bones and resist the body's defences.

The versatile super-agents can efficiently recognise any of these threats. To avoid releasing medicine before they reach the target site, they are dressed in 'special clothing', namely polymer coatings that help them recognise where to deliver their cargo.

For example, anticancer agents can sense contact with the rogue cancer cell receptors and, with the help of clinicians using ultrasound, ultraviolet light or magnetic signals, they know when to release the toxin inside the tumour cells.

In osteoporosis treatment, the nanoparticles could deliver molecules capable of silencing certain genes associated with the disease, to limit bone loss and promote bone formation. Ultimately, the tiny agents combatting infections could release their antibiotics to kill bacteria.

The project is running until 2021. More than three years since it kicked off, the project team have already filed two patents for their technology. They are also preparing to conduct clinical studies of the nanoplatform over the coming years. The application of a single technology for treating three different bone diseases – bone cancer, bone infection and osteoporosis – favours the industrial scale-up process. Ultimately, it could facilitate the transition of nanotechnology-based treatments (nanomedicines) from research to healthcare.

PROJECT
polyValent mEsopoRous nanosystem for bone DIseasesS

COORDINATED BY
The Complutense University of Madrid in Spain

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RESULTS PACK ON VIRUSES

In this Results Pack, we meet a number of EU-funded projects that are not only helping in the battle against COVID-19 but are also contributing to the wider virology field that will improve our overall understanding of viruses, as well as our ability to create even more effective antiviral treatments and vaccines.

Check out the pack at
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