BioEnredados

Uniendo Ciencia y Vida

Second Season - Volume 2

A production of:

CIC bioGUNE

MEMBER OF BASQUE RESEARCH & TECHNOLOGY ALLIANCE

EPISODES

Welcome to our podcast BioEnredados: Uniendo Ciencia y Vida!

We are your gateway to the cutting-edge research in biosciences that is taking place at the heart of CIC bioGUNE.

In each episode, we will immerse you in an exciting journey through the most innovative scientific and technological advances that are transforming our understanding of the biosciences, from basic chemistry to biology and medicine.

Our mission is clear: to bring you science in an accessible and exciting way. We aim to ignite your curiosity and nurture your interest in cutting-edge bioscientific research.

Are you ready?

TARGETED THERAPIES

NEW OPPORTUNITIES AGAINST CANCER

Cancer remains one of the leading causes of death worldwide and continues to present a major challenge for modern medicine. Despite remarkable advances in early diagnosis and the development of more effective treatments, cancer is still a highly complex disease. This complexity lies largely in its heterogeneous nature, there is not just one form of cancer, but hundreds, each with its own biological, genetic, and clinical characteristics.

While some types of cancer respond well to existing therapies, others quickly develop resistance, making them harder to treat and increasing the risk of relapse. This ability to adapt and evade treatment is one of the key reasons why cancer remains so difficult to control.

In recent years, targeted therapies have marked a significant step forward. A clear example is the use of monoclonal antibodies against the HER2 protein in certain types of breast cancer, which has substantially improved patient outcomes. Yet, these therapies are not a universal solution. Their effectiveness varies, and in many cases, tumors find ways to resist their effects.

To enhance the success of these treatments, research has turned to understanding cancer at the molecular level. Recent studies have shown that specific changes on the surface of cancer cells can influence how aggressive a tumor becomes and how it responds to therapy. These molecular modifications also affect how tumor cells interact with their environment, potentially playing a key role in treatment resistance and disease progression.

This deeper understanding opens the door to more personalized and effective therapies, ones that anticipate and counteract the strategies tumors use to survive. In this article, we explore these developments with Dr. **Ana Ruiz-Sáenz**, Ramón y Cajal and Ikerbasque principal investigator of the Cancer Therapy Resistance Group at CIC bioGUNE, whose research is helping to uncover how molecular changes in cancer cells can guide the next generation of targeted treatments.

Ana, breast cancer is the most commonly diagnosed cancer worldwide. While advances have improved survival, it remains a leading cause of death. What progress has been made in recent years in diagnosis and treatment?

- In terms of diagnosis, I'd highlight two key advances.

First, liquid biopsies, these are non-invasive tests that analyze tumor DNA in a patient's blood. They help detect relapses early and monitor how well a patient is responding to treatment. Second, the growing use of artificial intelligence in clinical settings is making it possible to detect tumors more accurately and improve diagnostic precision. We're already starting to see its impact in real cases, and this is likely

Right: Taken from Freepik image bank.

to grow in the coming years.

As for treatment, personalized medicine has made significant progress over the last few decades. Targeted therapies, such as CDK4/6 inhibitors and HER2-targeting antibodies, as mentioned earlier, have greatly improved outcomes for many patients. Immunotherapy is another important area, which works by boosting the immune system's ability to recognize and attack tumors. While these advances have changed the outlook for many patients, treatment resistance remains a major challenge.

We know that the development of targeted therapies, such as HER2 antibodies, has significantly improved outcomes for many patients. However, treatment resistance remains a major challenge. Why does this happen, and what strategies are being explored to overcome it?

- Resistance to treatment can happen in two main ways. Some tumors are intrinsically resistant from the start, but more often, resistance develops over time as cancer cells adapt to therapy. They evolve by acquiring mutations or activating alternative signaling pathways that allow them to survive.

Another challenge is tumor heterogeneity, not all cancer cells are the same. Some respond to treatment, while others resist and continue to grow. Fortunately, resistance often reveals new vulnerabilities that can be targeted with additional therapies.

That's why combination treatments are becoming more common. For example, HER2-positive breast cancer is now treated with two antibodies, trastuzumab and pertuzumab, plus chemotherapy. New approaches like antibody-drug conjugates and immunotherapy, especially in triple-negative cases, are also showing great promise.

"Antibody-drug conjugates (ADCs) function like Trojan horses, carrying chemotherapy directly into tumor cells to target them precisely while reducing side effects."

One of the most innovative aspects of your research is the study of glycosylation, the changes in the sugars that coat the surface of tumor cells. How does this process affect treatment effectiveness, and what new opportunities does it offer for developing future therapies?

- Yes, as you mentioned, glycosylation refers to the sugar layer that coats the surface of all our cells, much like a layer of leaves covering a vineyard. In tumor cells, this leafy coating is often altered, and these changes can affect how treatments work and how the cancer interacts with the immune system.

For instance, these sugar modifications can influence how well a drug binds to its target on the cell surface, such as the HER2 protein, and whether it can block it effectively. They can also impact how tumor cells communicate with immune cells, sometimes helping the cancer avoid detection.

In fact, research by scientists like Carolyn Bertozzi has shown that modifying this sugar layer can make it easier for immune cells to recognize and destroy tumor cells. These sugar structures act like tiny antennas for cellular communication, and when we learn how to rewire them, we open the door to smarter, more targeted therapies.

Right, up: Ana Ruiz-Sáenz, below: podcast episode cover.

You mentioned the work of Carolyn Bertozzi, a recent Nobel laureate, and we're seeing promising advances with therapies like the antibody-drug conjugates you mentioned earlier, which appear effective even in tumors with low levels of HER2. What do these discoveries mean for the future of cancer treatment, and what challenges remain?

- Antibody-drug conjugates (ADCs) like Enhertu have shown promising results in treating HER2-positive breast cancer and, notably, also in some patients with low HER2 levels, a breakthrough in targeted therapy. These drugs act like Trojan horses, delivering chemotherapy directly to tumor cells while minimizing side effects.

The key challenge now is identifying biomarkers to predict which patients with low HER2 will respond best, ensuring more precise treatments. Additionally, triple-negative and metastatic breast cancers remain difficult to treat due to their complexity, but ongoing research aims to make these conditions more manageable. While progress continues, there's still work ahead to improve outcomes for all patients.

BRAIN AT RISK

THE IMPACT OF PRIONS

Each year in Spain, approximately 1 to 2 cases per million inhabitants of transmissible spongiform encephalopathies (TSEs) are reported. These rare and ultra-rare diseases affect the brain and have a very low incidence, yet their impact is devastating. Patients experience rapid health deterioration, with symptoms such as memory loss, motor difficulties, and cognitive impairments, signs that can resemble more common conditions like Alzheimer's or Parkinson's disease.

TSEs belong to a group of neurodegenerative disorders caused by prions, misfolded proteins that induce other normal proteins to fold incorrectly as well. This misfolding leads to an accumulation of defective proteins in the brain, causing irreversible damage over time. Among the most well-known are Creutzfeldt-Jakob disease in humans, which results in rapid dementia, and the infamous "mad cow disease," which crossed the species barrier to infect humans through contaminated meat. In the Basque Country, cases of fatal familial insomnia have affected several families, presenting a significant public health challenge.

Understanding how prions work is essential to developing faster diagnostic methods and effective treatments. The questions researchers face include: What exactly are prions, and how do they damage the brain? Why is diagnosing these diseases so challenging? What progress has been made in early detection? And what new therapeutic strategies are being explored to treat and slow down their effects?

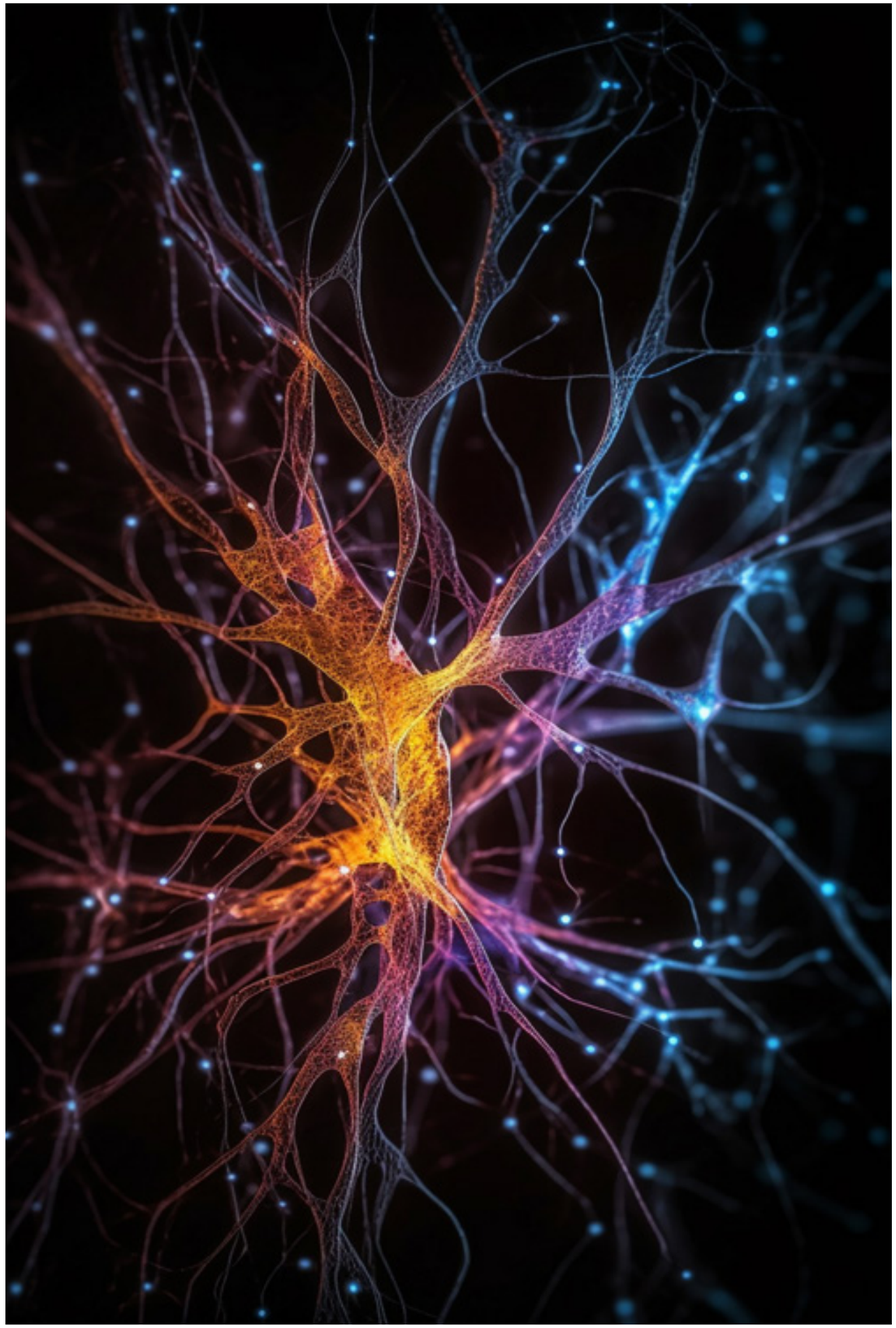
We seek answers to these fundamental questions with Dr. **Joaquín Castilla**, Ikerbasque research professor and principal investigator of the Prion Research Group at CIC bioGUNE, along with Dr. **Hasier Eraña**, researcher at Atlas Molecular Pharma, a company dedicated to developing therapies for rare and ultra-rare diseases.

Joaquín, Hasier, what exactly are prions and how do they differ from other agents that cause neurodegenerative diseases?

- Prions are infectious agents, but they are truly fascinating, not just because of the type of agent they are or the diseases they cause, but also due to their unique characteristics, size, and composition, which we'll likely discuss in more detail.

Prions are infectious proteins. Similar to the normal proteins found in all mammals, anchored to cell membranes in places like neurons. These proteins can, at some point, change their structure and become infectious. What makes prions unique is this structural change that gives them the ability to spread infection. Once a protein becomes a prion, it acts much like a microorganism by converting other normal proteins around it into the same infectious form.

This creates a cycle where newly converted proteins continue to transform others in their environment, perpetuating the process and leading to disease progression, which we will explain further.



Right: Image generated by AI, using Adobe Firefly.

We've mentioned that prions cause other proteins to misfold, but how exactly do they trigger this "domino effect," and how does it specifically impact brain function in those affected?

- We still don't fully understand how a normal protein becomes a harmful prion, but research shows that the misfolded, infectious form must come into contact with its healthy counterpart to begin spreading. This typically happens on the surface of neurons. The prion protein starts forming long fibers by recruiting and transforming nearby healthy proteins. These fibers eventually break apart, and each fragment can trigger the process again, creating a self-perpetuating cycle.

This chain reaction, known as prion-like propagation, begins slowly and silently, often progressing for years without noticeable symptoms. But once a critical point is reached, the disease advances very rapidly, often leading to death within months.

Interestingly, similar mechanisms have been observed in other neurodegenerative diseases like Alzheimer's and Parkinson's, where different proteins misfold and spread in a comparable way. However, each disease involves distinct proteins and brain regions, which is why symptoms vary. In prion diseases, depending on where the damage occurs, such as areas controlling speech, movement, or sleep, the symptoms can differ significantly. This makes diagnosis especially challenging, as prion diseases often mimic other brain disorders.

At the Prion Research Group at CIC bioGUNE, what progress is being made in understanding prion mechanisms, and how is this work helping to improve the diagnosis and treatment of these diseases?

- In our lab, we understood early on that to improve diagnosis and develop new treatments for prion diseases, we first needed to deeply understand how prions misfold and spread. To do this, we studied over a thousand proteins from different mammalian species to see which were more prone to spontaneous misfolding.

This research gave us valuable insights that we're now using to develop diagnostic tools based on detecting and amplifying early misfolding events. We've also identified certain "resistant proteins", found in species where prions don't misfold, which can block the harmful chain reaction. These resistant proteins could form the basis of a promising therapeutic strategy to stop disease progression. All of this reinforces the importance of early diagnosis, especially for diseases that develop silently over time.

"In our lab, we understood early on that to improve diagnosis and develop new treatments for prion diseases, we first needed to deeply understand how prions misfold and spread."

You've shared the research you're working on and the importance of early diagnosis in these devastating diseases, but what does the future look like when it comes to early detection and potential treatments?

- In recent years, we at CIC bioGUNE, along with researchers worldwide, have made important progress in understanding prion diseases, which has opened new paths for diagnosis and treatment. For a long time, the focus was on understanding how prions cause disease.

Now, thanks to this knowledge, we are exploring promising therapies.

One key approach we are testing involves reducing or eliminating the normal prion protein, which isn't essential and whose absence doesn't harm health in animal models. By doing this, the harmful prions have nothing to infect and spread. Another approach blocks the interaction between normal and misfolded proteins to stop disease progression. Our team is combining these strategies using resistant proteins that replace the normal ones and prevent prion spread.

Early diagnosis is vital, as prion diseases are often found too late. We're improving RT-QuIC, a technique that detects tiny amounts of prions early. It's already used in hospitals and shows promise for diagnosing diseases like Parkinson's and Alzheimer's.

Although prion diseases are rare, our research helps reveal mechanisms that could apply to more common conditions, offering hope for better treatments across the board.

Right, up: Joaquín Castilla and Hasier Eraña, below: podcast episode cover.

CUSTOM PROTEINS

ARTIFICIAL INTELLIGENCE TO TRANSFORM THE FUTURE

In recent years, artificial intelligence (AI) has transformed the way we understand and manipulate some of the most fundamental biological processes. One of the most promising, and simultaneously challenging, areas is protein design. This involves the ability to modify existing proteins or create entirely new ones that do not exist in nature, with specific functions tailored to address urgent real-world problems.

Imagine enzymes engineered specifically to break down plastics polluting our oceans, or proteins designed to capture carbon dioxide from the atmosphere to help combat climate change. What if, instead of relying on generic treatments, we could develop proteins tailored to create personalized therapies for individual patients?

What once seemed like a distant dream is now becoming a reality thanks to advanced AI tools such as deep learning models, evolutionary algorithms, and sophisticated computational simulations. These technologies enable scientists not only to predict with remarkable accuracy how proteins fold into their three-dimensional shapes, but also to design new protein sequences with desired structures and functions, tasks that previously required years of trial and error in the laboratory.

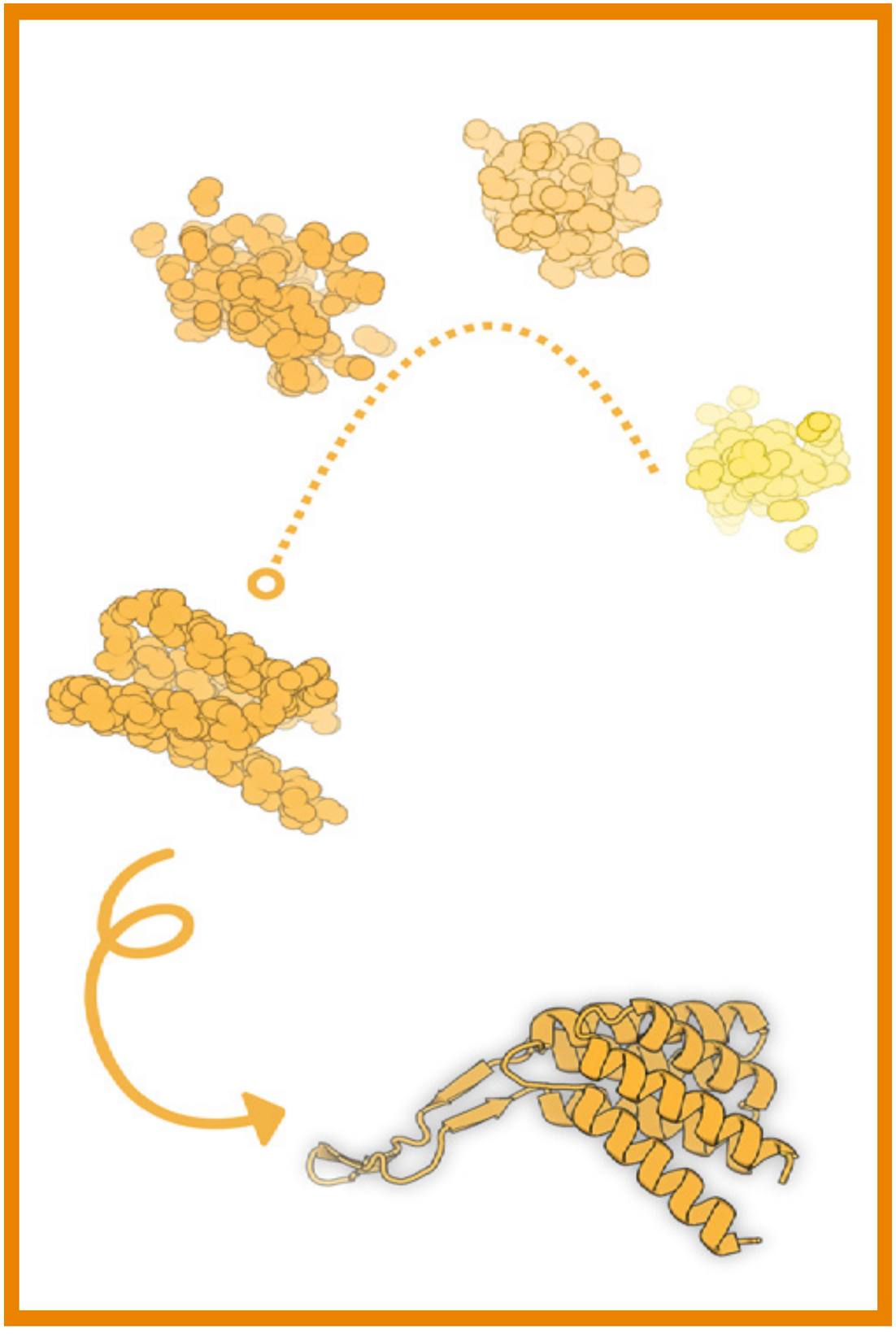
Artificial intelligence plays a central role in this process, accelerating discovery and expanding the possibilities of what protein engineering can achieve. Researchers now use cutting-edge AI methods to predict protein behavior and design novel molecules, opening the door to innovative applications in medicine, environmental science, and beyond.

Guiding us through this cutting-edge research is Dr. **Reyes Núñez**, postdoctoral researcher in the Computational Chemistry group at CIC bioGUNE. Her work sheds light on the tools, challenges, and exciting practical applications of AI-driven protein design.

Reyes, in the first episode of this season, we discussed proteins and their essential roles in living organisms. To refresh our readers' memory, could you briefly explain what proteins are? And how does the design process work, especially considering it was once such a challenging task?

- As mentioned, proteins are the machines and tools of cells. They carry out almost all essential functions in living organisms. Proteins are chains of amino acids that fold into precise 3D shapes, and that structure determines their function, like puzzle pieces that only fit certain roles, from cutting molecules to fighting viruses.

That's why understanding a protein's structure based on its amino acid sequence is so important. It helps us know how it works and how we might modify or design new ones.



Right: Image created by Reyes Núñez.

Protein design flips this process. Instead of going from sequence to structure, we start with a desired function, figure out the needed structure, and then design a sequence that folds into it. Like starting a book from the end.

This used to be incredibly difficult. But with recent advances in AI and computational tools, we're now designing proteins from scratch, something that seemed like science fiction not long ago.

And none of this would be possible without the decades of work by scientists who determined protein structures experimentally, mainly through X-ray crystallography, and built the Protein Data Bank. That data made today's AI breakthroughs possible.

Digging a bit deeper into the design process, how exactly is it carried out? What AI-based tools and methods are used to create proteins with specific functions?

- Yes, so it's important to distinguish between two approaches: one is designing entirely new proteins from scratch, and the other is modifying existing natural proteins to enhance their properties. Today, let's focus on the design of new proteins.

The first step is generating the 3D structure that will carry out a specific function. AI tools, mainly using diffusion methods, help with this. These models start with random noise, like a cloud of points, and gradually "sharpen" it into a defined protein structure. It's very similar to how AI image generators work.

Once the structure is defined, the next step is designing the amino acid sequence that will fold into that exact shape. This also uses deep learning-based tools. Then we verify that the sequence actually folds into the intended structure, again, using AI, including well-known tools like AlphaFold.

"Our custom mini-proteins bind selectively to larger surfaces, reducing side effects and boosting effectiveness, creating precise 'keys' for 'locks' to improve cancer treatments."

These breakthroughs have been so impactful that in 2024, David Baker, John Jumper, and Demis Hassabis were awarded the Nobel Prize in Chemistry for structural prediction and protein design.

On a personal note, I had the incredible opportunity to work in David Baker's lab a few years ago and learn these methods firsthand. Now, at CIC bioGUNE, we're applying them at scale. Thanks to our strong computing capabilities, we can generate thousands of designs quickly, amino acid sequences in seconds, structures in minutes, long before testing anything in the lab.

That speed means what once took years can now be done in a day. We can explore and test far more protein candidates than ever before.

In the Computational Chemistry lab, you're working on several projects related to protein design. Could you share a few examples of how these methods are being used to solve real-world problems?

- One of our projects focuses on designing mini-proteins to improve CAR-T cancer immunotherapy. The goal is to block a specific receptor protein linked to better treatment response.

Right, up: Reyes Núñez, below: podcast episode cover.

Traditional small molecules struggle with specificity because the receptor has many similar versions in the body. Our custom-designed mini-proteins bind more selectively and strongly by targeting a larger surface area, reducing side effects and improving effectiveness.

In short, we're creating highly tailored "keys" for specific "locks" in the body, offering a smarter, safer way to enhance cancer treatments.

Finally, what are the main challenges we still face in AI-driven protein design? And looking ahead, how do you see this technology evolving and impacting fields like healthcare, the environment, and biotechnology more broadly?

- A key challenge in AI protein design is predicting interactions with small molecules. AI handles static structures well but struggles with flexible regions, like those in antibodies, because of limited interaction data. AI is quickly transforming healthcare, environmental science, and biotech by speeding up protein design and making it more precise. It's a valuable tool that's accelerating research and innovation across many fields.

INVISIBLE MESSENGERS

EXOSOMES AND THEIR ROLE IN HEALTH

Communication is fundamental to all living beings, even within our own bodies. Imagine, then, the inside of the body as a vast microscopic ocean. In this sea, cells are like islands, constantly exchanging messages. But instead of voices or signals, they send tiny packages called exosomes, much like messages in bottles traveling across the waves with a precise destination.

These microscopic vesicles carry important cargo: proteins, lipids, RNA, and other molecules that can change how recipient cells behave; activating, protecting, or even sometimes contributing to disease. Exosomes act as a sophisticated biological postal system, playing a key role in cell-to-cell communication.

The study of exosomes is revolutionizing medicine, opening new possibilities for earlier diagnoses and more targeted treatments in diseases such as cancer, liver disorders, and neurodegenerative conditions. These vesicles act as natural messengers that influence cellular behavior and, thanks to their ability to carry precise information, hold great potential as therapeutic delivery vehicles in the future.

To better understand the remarkable role of exosomes, we turn to CIBERehd researchers, Prof. **Juan Manuel Falcón**, Principal Investigator of the Exosomes Group at CIC bioGUNE, and Dr. **Félix Royo**, postdoctoral researcher on the team. Drawing on their expertise, we will explore how these microscopic vesicles serve as crucial communicators between cells, offering promising insights for early diagnosis and innovative treatments for diseases like cancer, liver conditions, and neurodegenerative disorders.

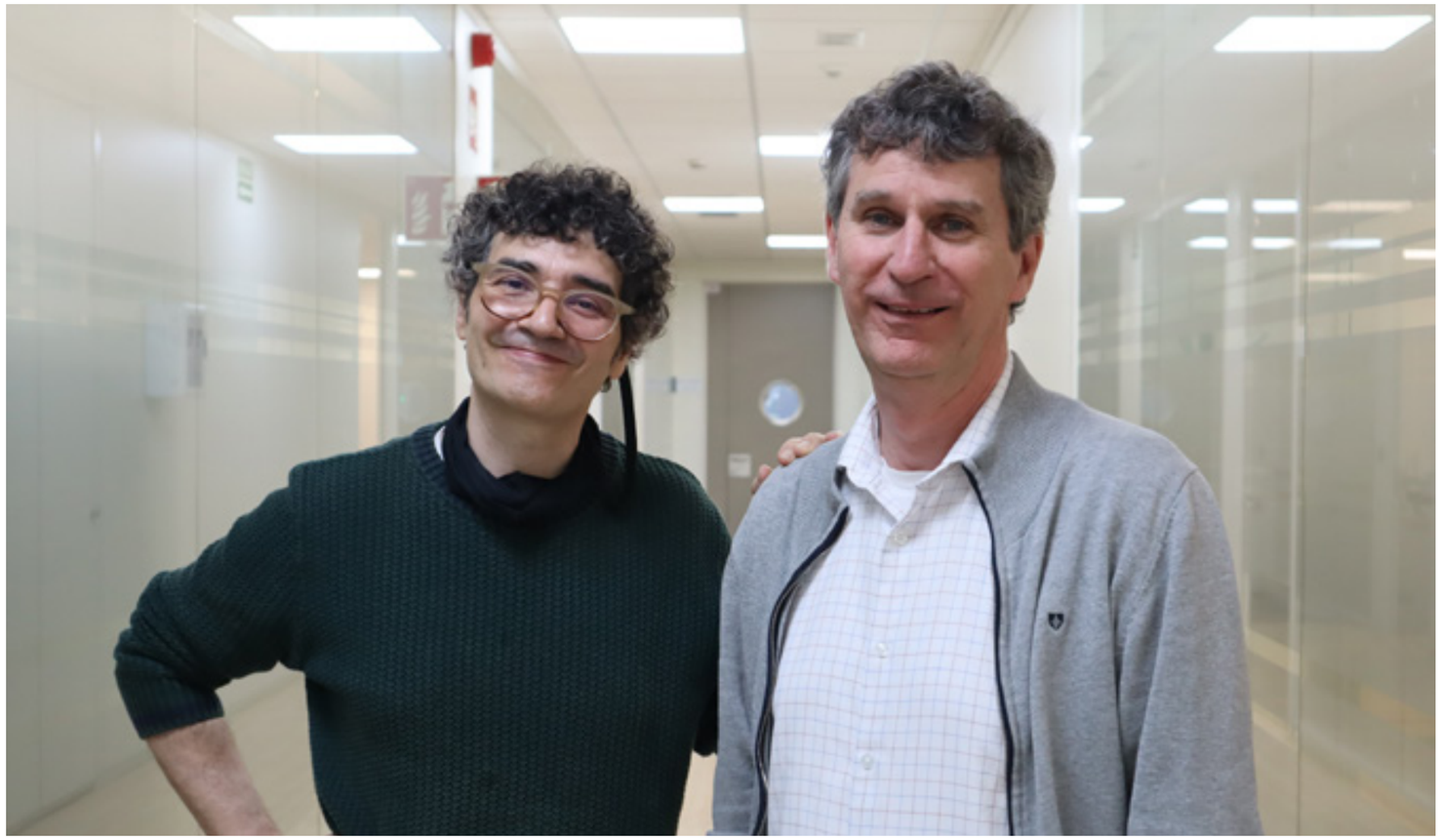
What exactly are exosomes, and why should we pay attention to something so tiny?

- One of the main challenges with exosomes is their incredibly small size. They're so tiny that they can't be seen with a regular optical microscope, which means we need specialized technologies to detect and classify them. This has been a major focus in the field, developing methods to properly identify and differentiate these vesicles.

At CIC bioGUNE, we were among the first to visualize exosomes with their characteristic double membrane and spherical shape, using electron microscopy in collaboration with Navigil. In 2008, we published the first detailed images of exosomes secreted by liver cells, a milestone that helped reveal their structure and composition.

Since then, the discovery of many different types of vesicles has made their study more complex. Our group has contributed by developing new methodologies and driving technological advances that are essential for classifying and better understanding exosomes. Gaining this knowledge ultimately gives us more power to unlock their potential.

Right: Image generated by AI, using Adobe Firefly.



Additionally, we have made significant contributions internationally by applying molecular techniques such as proteomics and metabolomics. These approaches have allowed us to analyze the contents of these tiny "messages" that cells send, providing valuable insights that could be critical for identifying new biomarkers and advancing medical research.

How do our cells communicate through exosomes? What kind of information do these tiny vesicles carry?

- Cells communicate through exosomes by secreting thousands of these tiny vesicles, like messages in bottles, that travel through the bloodstream or other fluids until they reach a target cell. That cell has receptors that recognize the exosome, take it inside, and "read" the information it carries. The cell then follows the instructions encoded in the exosome, coordinating responses with other cells.

Initially, exosomes were thought to be just cellular waste, but we now know they carry important cargo like nucleic acids and active enzymes, which allow them to influence the environment around them during their journey. These vesicles can modify tissues and fluids, playing roles in both normal body functions and diseases. For example, in neurodegenerative diseases like prion disorders, exosomes help spread harmful proteins across the brain.

So, exosomes are not just passive messengers; they actively participate in communication by carrying catalytic enzymes and signaling molecules, making them crucial players in health and disease.

From your research group at CIC bioGUNE, what studies are you currently conducting on exosomes?

- We've found that exosomes not only travel through the body but also transmit signals that influence disease progression. At CIC bioGUNE, our group collaborates with hospitals studying diseases like cancer, metabolic disorders, neurodegeneration, and schizophrenia. We analyze exosomes' molecular and structural differences to understand their role in disease development and therapy monitoring.

A key challenge is deciphering how exosomes target specific cells. Once we understand this "address code," we could use exosomes to deliver drugs precisely where needed. Our work focuses on identifying the surface molecules that allow cells to recognize and internalize exosomes, aiming to harness this for targeted therapies tailored to different diseases.

Finally, what potential do exosomes hold for the future of biomedicine? And what are the main challenges this field currently faces?

- We believe that what the exosome field still lacks is an approved vesicle-based drug. While diagnostic methods using vesicles are already available, a truly approved medication, whether by the FDA or European agencies, that utilizes vesicles is still missing. Our prediction, as mentioned before, is that such a drug will either involve vesicles loaded with chemotherapeutics targeted directly to tumors or focus on tissue regeneration.

The regenerative potential of vesicles is especially promising. To clarify, regeneration means, for example, that applying exosomes to a wound can speed up and improve healing. In cases of liver damage, vesicle-based therapies help reduce oxidative stress when blood flow returns, protecting the cells. So, the real challenge for us is bringing such a drug to pharmacies.

We also emphasize that many regenerative therapies using cells actually work because the exosomes secreted by those cells carry the healing power. This reduces concerns about using whole cells, which may have complications, while exosomes offer a safer alternative with similar benefits.

Exosomes are gaining attention in academia and cosmetics, especially Korean skincare, for their regenerative benefits. Within the International Society for Extracellular Vesicles, we stress the need for strict purification and quality control, as many products labeled "exosome-based" lack pure exosomes. Proper standards prevent misattributing failures, and while promising, the field still needs more time, protocols, and better technologies to mature.

"A key challenge is deciphering how exosomes target specific cells. Once we understand this "address code," we could use exosomes to deliver drugs precisely where needed."

Right, up: Juan Manuel Falcón and Félix Royo, below: podcast episode cover.

UBIQUITINS AND RECYCLING

THE ENGINE OF CELLULAR LIFE

Inside every one of our cells, something remarkable is happening, a silent choreography of molecules that keeps life going. Imagine for a moment that the cell is like a bustling city. There are factories constantly producing goods, delivery trucks moving materials from place to place, and, crucially, sanitation crews that keep everything clean and running smoothly. Without those crews, the city would fall into chaos. The same is true inside us: when the cell's cleanup systems fail, things can go terribly wrong.

At the center of this inner order lies a tiny, almost invisible player: ubiquitin. It may sound technical, but think of ubiquitin as a molecular tag, a kind of sticky note that tells the cell what to do with a particular protein. "This one is broken," it might say. Or, "this one's job is done, recycle it." It's a system as elegant as it is essential, allowing cells to label and sort their contents with extraordinary precision.

And yet, this system doesn't just handle trash. It keeps the cell in balance, helps it adapt and protects it from disease. When the process goes wrong, the consequences can be devastating. One tragic example from history is the story of Thalidomide, a drug once thought safe, later linked to severe birth defects. Only decades later scientists discover it was interfering with the cell's protein control system, disrupting development at the molecular level.

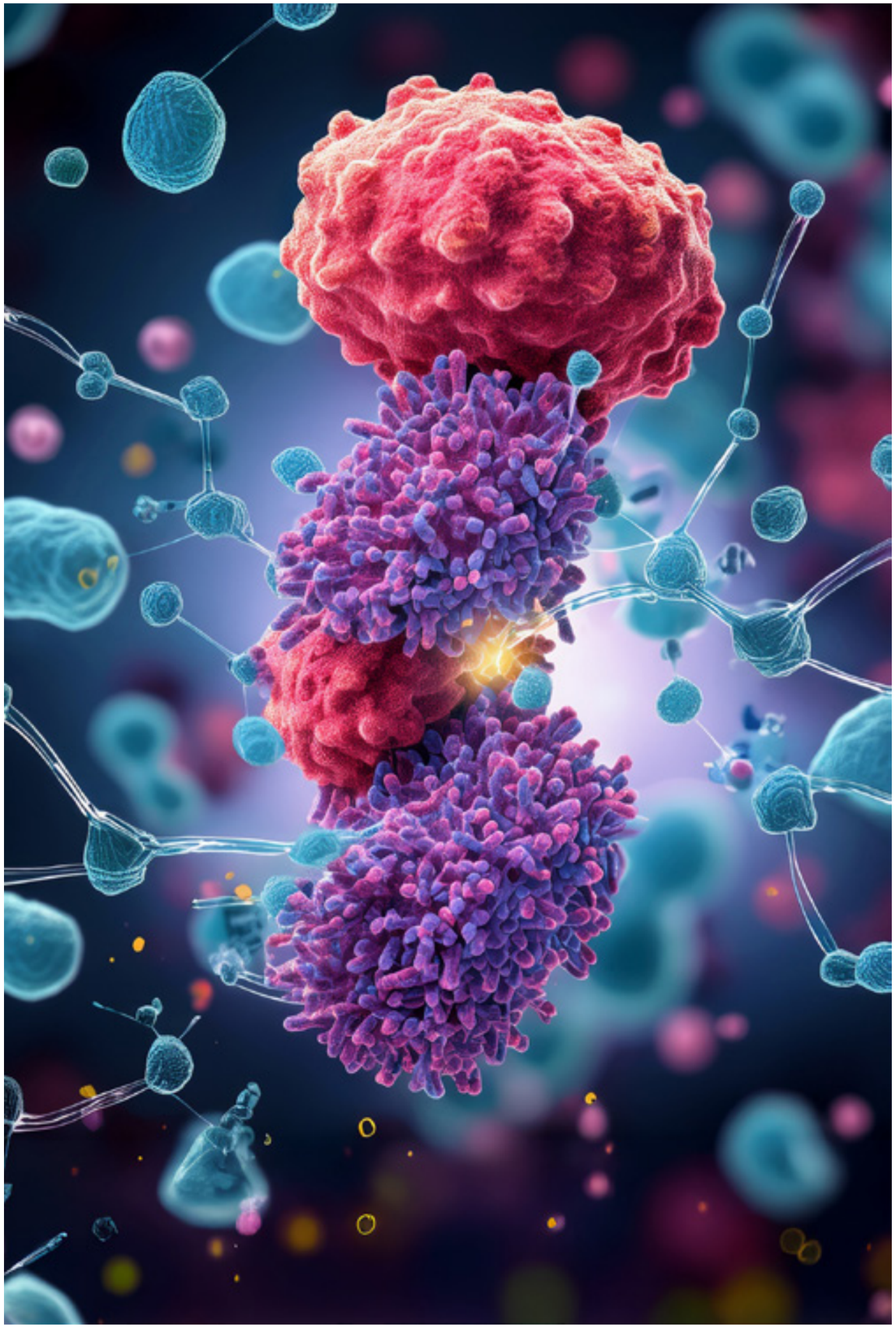
What we're learning now is that ubiquitin isn't just a label, it's a language. And if we can learn to read and write in it, we might find new ways to heal, to repair, and to understand life itself.

To explore these questions further, we are joined by Dr. **Rosa Barrio**, Principal Investigator in the Ubiquitin-likes And Development Lab at CIC bioGUNE. With her extensive expertise, she will guide us through how disruptions in protein regulation lead to disease and how unraveling the mysteries of ubiquitin could pave the way for new approaches to understanding and treating illnesses.

What are ubiquitins, and what role do they play in maintaining protein balance, or proteostasis, within our cells?

- Ubiquitins are a small family of proteins, tiny in size but essential in function. Acting like molecular tags, they attach to other proteins to tell the cell what to do with them. Often, they mark proteins for recycling, but sometimes they direct them to move elsewhere or interact with other molecules.

At first, ubiquitins were nicknamed "the kiss of death," as scientists thought their only role was to label proteins for destruction. The name "ubiquitin" reflects how common they are in all cells. Early on, it seemed their main job was to send unwanted proteins to the cell's recycling center, the proteasome.



Right: Image generated by AI, using Adobe Firefly.

But over time, researchers discovered a much more complex story. Ubiquitins can form different chains, and each combination sends a unique signal. This is now known as the "ubiquitin code," a cellular language that decides the fate of proteins. A whole set of helper proteins reads and acts on these instructions.

Scientists are still decoding how this system works and what each tag means. A powerful example of its importance is the case of Thalidomide. Given to pregnant women to ease nausea, it later caused severe birth defects. Decades on, it was revealed that thalidomide disrupted protein regulation through the ubiquitin system, showing just how vital and sensitive this process is.

What happened with Thalidomide? How did it affect this cellular system, and how was its true mechanism of action uncovered years after its clinical use?

- It's a simple yet powerful story. Thalidomide, a drug once prescribed to relieve nausea during pregnancy, tragically caused severe birth defects, consequences that many people still live with today. From the 1960s until as late as 2011, the true reason behind its devastating effects remained a mystery. It wasn't until much later that scientists discovered its target: a protein called cereblon.

Cereblon plays a key role in the ubiquitin system as part of an enzyme complex known as an E3 ligase, molecules responsible for attaching ubiquitin tags to specific proteins. Thalidomide disrupts cereblon's normal function, causing it to tag the wrong proteins for degradation. Among these are crucial factors needed for proper limb development in embryos. One essential protein was broken down too early in the presence of Thalidomide, which helps explain the limb malformations. This critical insight didn't emerge until 2018, decades after the drug's initial use.

It's a tragic example with profound human consequences, but it also sheds light on the deep importance of the ubiquitin system in human development and disease.

Right, up: Rosa Barrio, below: podcast episode cover.

"Thalidomide is a tragic example with profound human consequences, but it also sheds light on the deep importance of the ubiquitin system in human development and disease."

From your research group at CIC bioGUNE, how do you study the proteostasis system? What are its implications for disease or the development of new treatments?

- We focus on understanding how the cell's protein regulation system or proteostasis, works, and how its disruption can lead to disease. We study it using model organisms like the fruit fly (Drosophila melanogaster), which helps us explore how ubiquitin affects development from embryo to adult. We also develop new tools to better observe how ubiquitin tags proteins, a fast and reversible process that happens constantly in the cell and is often difficult to study.

Our work connects directly to the growing field of targeted protein degradation, which is gaining momentum in drug development. The case of Thalidomide, which unintentionally interfered with a key protein-tagging enzyme, gave researchers an important clue: what if we could harness this mechanism to deliberately remove harmful proteins, like those driving cancer? This idea led to a new generation of therapeutic molecules, known as PROTACs, some of which are already in clinical trials. We're excited to contribute to this promising direction, where understanding the cell's recycling system could lead to smarter, more targeted treatments.

Finally, what are the biggest challenges and opportunities currently facing research in this field?

- Selective protein degradation has sparked exciting interdisciplinary research, involving biologists, chemists, physicists, and clinicians. While we've made progress, much about how this system works in different cells remains unknown. New findings suggest other molecules like sugars and lipids may also be involved, adding complexity.

This journey started with basic science and has led to important discoveries and potential therapies. At CIC bioGUNE, understanding these fundamental processes is crucial for developing future treatments.

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EXCELENCIA SEVERO OCHOA

EUSKO JAURLARITZA GOBIERNO VASCO

Established in 2004 under the auspices of the Basque Government, CIC bioGUNE is dedicated to advancing biomedical science. Its interdisciplinary team of over two hundred scientists and technicians delves into the molecular foundations and mechanisms of diseases, aiming to innovate in diagnostic methods and foster the advancement of innovative therapies.

Recognized as a Severo Ochoa Center of Excellence, CIC bioGUNE leads cutting-edge research at the intersection of Biology, Chemistry, and Mathematics, focusing on Cancer, Rare Diseases, Infectious Diseases, and Metabolic Disorders. Our infrastructure includes advanced technological platforms that support scientific discovery and collaboration, positioning us among Europe's foremost research institutes.

We are committed to bridging the gap between complex scientific research and public understanding through diverse outreach activities. By translating our research into accessible language and engaging the community in scientific advancements, we emphasize the importance of investing in research for societal progress and well-being. These efforts not only strengthen our connection with stakeholders but also promote broader appreciation and engagement with science for the benefit of society.

Transcriptions, editing and layout:

These podcast episodes have been transcribed, translated, edited, and formatted for this magazine by **Jana Sendra Viscarro**.

"Cutting-edge science advancing at the frontier between Chemistry, Structural, Molecular and Cellular Biology, aiming to develop a more Precise Medicine for the future"

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CIC bioGUNE

Parque Científico y Tecnológico de Bizkaia
Edificio 801 A
48160 Derio, Bizkaia, España

Tel.: +34 944 061 300
www.cicbiogune.es