

BioEnredados


Uniendo Ciencia y Vida

First Season - Volume 1

A production of:

CICbioGUNE

MEMBER OF BASQUE RESEARCH
& TECHNOLOGY ALLIANCE



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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?

SCIENCE OR SCIENCE FICTION

AI ON THE SCIENTIFIC HORIZON

At the threshold of a new horizon, a world in constant evolution unfolds before us, a scenario where the boundaries between science and fiction blur ever more. We find ourselves amidst a revolution, where artificial intelligence stands as the undisputed protagonist, transforming disciplines such as biology, chemistry, and medicine on its path towards a promising future.

Artificial intelligence, a branch of computer science, focuses on developing machines or programs capable of simulating or imitating human intelligence to solve problems efficiently and automatically. Based on algorithms and mathematical models, AI allows machines to learn from data, adapt to the environment, and improve their performance as they gain more experience. In a moment marked by the debate on the ethics and security of this technology, artificial intelligence has been positioning itself imperceptibly in our daily lives, turning science fiction into a tangible reality.

In this journey into the unknown, we delve into a universe where artificial intelligence and scientific research

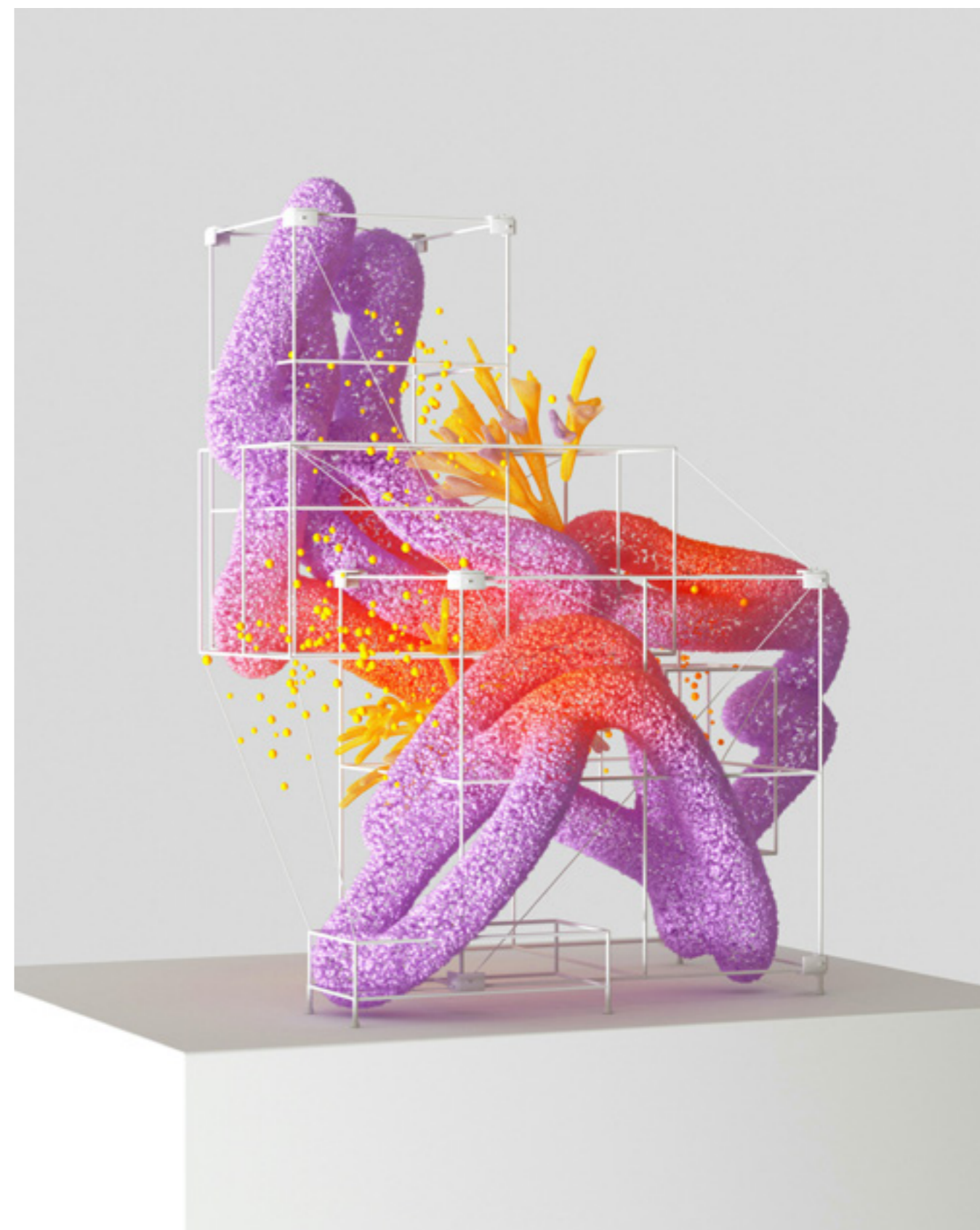
converge, challenging the limits of what is possible and opening new horizons of knowledge. What are the milestones marking this path towards the future? How is artificial intelligence revolutionizing our way of investigating and addressing the most pressing challenges of our society? And above all, what consequences will this technological revolution have on the development of innovative therapies and medications?

To delve into this thrilling territory, we are joined by **Gonzalo Jiménez-Osés**, Ikerbasque Professor and leader of the Computational Chemistry group at CIC bioGUNE. From his privileged perspective, Dr. Jiménez-Osés invites us to explore the latest advances and the challenges that still persist in this exciting field, offering us a unique insight into how artificial intelligence is transforming the face of contemporary science.

Could you give us a little overview of how artificial intelligence is being integrated into science?

- The integration of artificial intelligence is happening quickly and somewhat on the fly because its progress has been rapid and has caught many of us off guard. Especially in the scientific world, it's something we hadn't experienced much before, but the developments have mainly been carried out in software and communication companies. So, it's been a bit surprising that the most prominent developments, like AlphaFold or ChatGPT-3, have appeared almost overnight, in a broader context.

So, we're adapting on the fly. From my personal experience, I can say that this integration has been extremely fast, simple, and effective. In my field, there's a steep learning curve for the physics-based methods we used to determine molecular



Right: Pexels image bank.



molecular properties, which has been a barrier for students. Paradoxically, the adoption of these technologies has been rapid and straightforward, perhaps because they are quite opaque in their internal workings.

In our group, we're incorporating these technologies into our developments on a week-to-week basis. This marks a significant change because we no longer have to wait years for a new version of a program or an update, but literally every week or month, improved versions or competitors appear. Adaptation is virtually in real-time.

Could you tell us what your research is based on and how this technology has been applied in your field?

- Our research focuses on computer simulation of chemical and biological processes, ranging from basic chemistry to complex biological processes.

We utilize tools like AlphaFold, a groundbreaking neural network for predicting protein structures. This has enabled us to solve problems previously considered unsolvable in record time. Additionally, we explore neural networks like ProteinMPNN. By integrating these tools, we design new proteins with functions not found in nature, such as metal-based catalysts or blockers for certain proteins.

What used to take us years is now accomplished in a matter of weeks, thanks to the speed and precision of these AI-based tools. This has significantly accelerated our work, allowing us to progress towards laboratory experimentation much faster.

How do you envision artificial intelligence influencing, for example, the development of personalized medicines or therapies, now that it provides a speed that didn't exist before?

- Exponentially. There are two main areas in drug design: small molecules and protein-based molecules. Artificial intelligence is accelerating drug discovery, particularly in designing protein-based inhibitors, yielding remarkable results.

AlphaFold provides the structure of every protein in the genome, enabling drug design against previously unknown targets and creating entirely new drugs rapidly.

Google and other companies are creating spin-offs focused on drug development, indicating a significant shift in the industry. However, the challenge lies in standardizing data across various scientific fields to ensure the reliability of neural network predictions.

How do you think teaching in scientific fields should adapt to include understanding of this technology and its proper use?

- It's a necessity and a challenge, as the field is constantly changing. For example, technologies like ChatGPT or AlphaFold, based on architectures like the transformer developed by Google, are constantly evolving. It's difficult for chemists, physicists, doctors, and biologists to understand these technologies, but we can use them.

I believe education should progress at two speeds. From the early years of training, it's essential to incorporate programming,

“What I do know is that we must not be afraid and face this technology with an open mind, knowing that not every prediction from artificial intelligence is correct or valid.”

especially in Python, which is the primary language in the development of these technologies. Additionally, solid knowledge of neural network architectures and data processing is required. All scientific students should have this knowledge in a cross-sectional manner.

How do you envision this collaboration evolving in the future and how do you think it could influence our society?

- I don't dare to make predictions because reality always surprises us. Everyone talks about technologies like ChatGPT-3, Diffusion, or Dali, which allow you to do things in real-time with exquisite quality, and this has caught us by surprise.

What I do know is that we must not be afraid and face this technology with an open mind, knowing that not every prediction from artificial intelligence is correct or valid. Critical thinking is essential. We'll see how everything unfolds, but I believe changes will happen quickly, and job profiles will transform.

Right, up: Gonzalo Jiménez-Osés, below: podcast episode cover.

LIVER ALERT!

THE SECRETS OF THE LIVER

The liver, that amazing and vital organ that often goes unnoticed, is the true protagonist in the complex scenario of our digestive system. Did you know it's the largest organ in this wonderful machinery that is our human body? Larger than the heart and almost as heavy as a soccer ball, the liver arouses fascination for its ability to perform such a crucial task for our health.

What is its exact role in digestion and nutrient absorption? Well, this is where the magic of the liver truly shines. This little giant unfolds like an internal cleaning engine, tirelessly working to metabolize the substances we consume daily. Imagine it as an elaborate chemical laboratory inside our body, breaking down what we eat and drink to turn it into useful nutrients, while eliminating the waste and toxins our body doesn't need.

But, how does the liver accomplish this amazing task? That's a question that has puzzled scientists and curious minds for a long time. And it's because, essentially, the liver is a marvel of biology. From the food we eat to the air we breathe, everything passes

through the liver's filter. Our daily diet has a direct impact on its functioning, and it's crucial to understand how our food choices can influence the health of this vital organ.

And here's where a serious topic comes into play: alcohol consumption. Did you know it can have serious consequences for the health of our liver? The liver, despite its amazing regenerative capacity, has its limits. Excessive alcohol can damage liver cells, leading to serious conditions such as liver cirrhosis.

To delve deeper into this topic, we have invited an expert in the field: **Malu Martínez-Chantar**, principal investigator of the Liver Diseases group at CIC bioGUNE. With her experience and knowledge, she will help us unravel all the secrets of the liver and understand how we can better care for it in our daily lives.

Could you give us a general overview of this organ and its functioning?

- The liver is one of the largest organs in the digestive system and plays a fundamental role every day. The liver will have a very important role, for example, in lipid metabolism. All the fats we ingest will be metabolized by the liver to prevent those lipids from staying in the liver and causing damage to the liver, our cells, and ending up with what we'll talk about later, a fatty liver.

For example, the liver will also play a very important role in the immune system. It will also have a very important function in the formation, for example, of bile acids which are responsible for generating that bile that will degrade that metabolism. And then, above all, it has a very, very essential role in maintaining constant glucose levels.

Glucose levels have to be kept constant throughout the day, okay? So that we don't have very significant drops or increases in

Right: Polina Tankilevitch,
taken from Pexels image
bank.





glucose. And the liver will be responsible for maintaining that glucose. And finally, the liver will metabolize all our toxins that we take every day.

We ingest medicines, we ingest alcohol, we ingest nutrients, we ingest fats and the liver will be responsible for metabolizing all those toxins and secreting them and eliminating them.

What role does the liver play in digestion and nutrient absorption, and how do our eating habits affect the liver?

- The liver, all of this is a balance between eating too much or too little and eating well, right? When we, for example, ingest a lot of fats, then the liver has to make an extra effort to metabolize those fats because, if those fats stay in the liver, they will produce damage to the cells. So, the liver tries in some way to metabolize, eliminate those fats so they don't stay in the liver.

If we take, for example, a diet very rich in carbohydrates or sugary drinks, what happens? We are ingesting a lot of glucose. That glucose, in the end, will also be converted into fats and then, again, the liver has to make an extra effort to remove and eliminate those fats and prevent damage to the liver from occurring. If we ingest alcohol, a very specific alcohol metabolism will occur and we know that deeply damages our cells.

The liver has a great capacity of regenerating itself. That means it is capable of forming more cells, okay? We cause damage and suddenly another healthy cell appears that occupies the place of that cell we have damaged. But there may come a time when the damage is excessive, the regenerative capacity of the liver is not enough to prevent all the damage we have done.

Right, up: Malu Martínez-Chantar, below: podcast episode cover.

And that's where liver disease begins. The most prevalent disease is fatty liver, which is associated with obesity, metabolic syndrome, it is estimated that 25% of the general population suffers from fatty liver. While it can be reversed with lifestyle changes, some patients progress to advanced stages, potentially leading to fibrosis, cirrhosis, and liver cancer.

What are the current scientific advancements in treating liver conditions?

- For instance, in fatty liver, you're probably aware of a medication many people are taking, especially for obesity and insulin resistance. This treatment has shown a significant impact on fatty liver by addressing these underlying conditions.

Additionally, while there's no specific treatment for alcohol, current approaches focus on managing associated health issues. Given the prevalence and mortality rates linked to liver pathologies, there's a pressing need for research to explore new therapeutic avenues.

What are the next steps in research and how could they impact prevention?

- Well, first of all, you know there's a huge effort towards personalized medicine. I think it's one of the key aspects that we need to highlight. Personalized medicine aims to

“By 2030 there will be countries with almost 35% of patients with fatty liver, so of course eating well and eating healthy. I think that's something that needs to be taught from schools, really.”

tailor, as its name suggests, the treatment we give to patients in a very specific way to what we have in front of us. So, the first thing we need to do is to deeply understand the mechanisms underlying liver pathology.

That is, if we know very well what is happening to that patient, then we'll have much more chances of blocking or modulating the pathways that are altered in a much more efficient way than if we haven't characterized that pathology and we're just throwing bombs to see where we can hit. So, targeted therapy, well, with that, we save time, which is very important in this type of pathologies, and probably the likelihood of being effective and successful is much higher. So that's one side, personalized medicine, of course.

Prevention is very important. Especially, as I mentioned, if we're dealing with fatty liver with a prevalence of 25%, it's expected that by 2030 there will be countries with almost 35% of patients with fatty liver, so of course eating well and eating healthy. I think that's something that needs to be taught from schools, really.

DNA REVEALED:

DECIPHERING OUR HERITAGE

In the fascinating world of future medicine, we delve into a territory as vast as it is mysterious: that of our own genes. Have you ever wondered how they influence our health and predisposition to diseases? Would you like to discover how science is revolutionizing medicine by designing personalized treatments for each individual?

We immerse ourselves in the depths of integrative genomics, a discipline that allows us to understand how our genes and our lifestyle interact to influence our health. From the very roots of diseases to the ability to predict our risk of developing them, we embark on a journey of discovery.

Imagine being able to unveil the most intimate secrets of our biology, understanding the subtle connections between our genes and our way of life. Here, we explore how integrative genomics allows us to piece together the complex genetic puzzle, thus revealing the secrets encoded in our DNA.

Are you ready to explore how science can shape a future where medicine adapts to each of us? What impact will decoding the

genetic code have on our quality of life and longevity?

To delve into this fascinating topic, we have the expertise of **Urko Martínez Marigorta**, Ikerbasque Research Professor of Integrative Genomics at CIC bioGUNE. Join us on this journey to the frontiers of tomorrow's medicine.

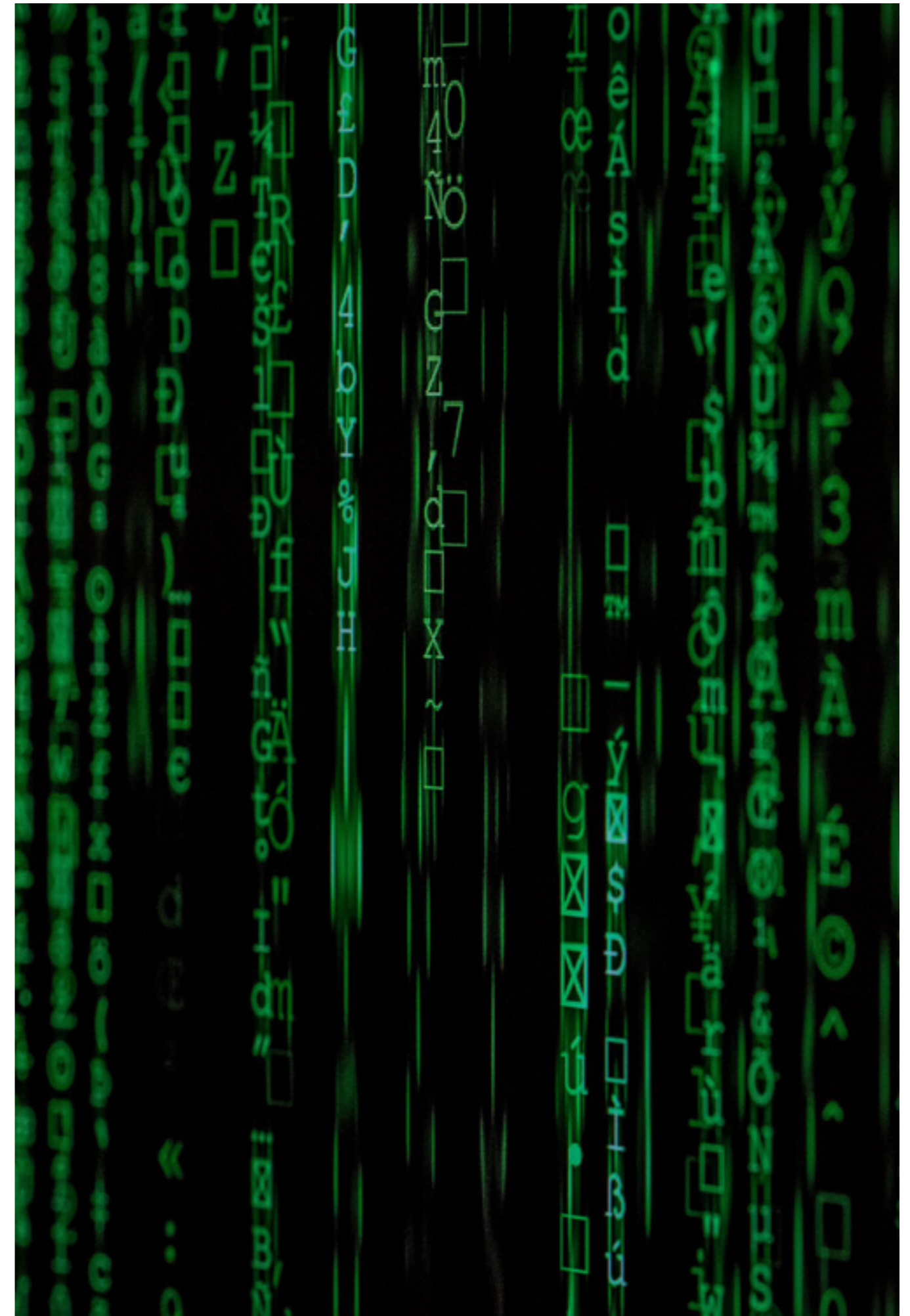
Could you explain in simple terms what this study of the genetic basis of diseases entails and how you are approaching these investigations?

- I believe that in order to understand what we are doing in genomics research, it's good to distinguish between two types of diseases. Typically, we have what we call hereditary diseases, which are the classic diseases where we notice certain families have an accumulation of people with the disease, such as hereditary breast cancer or, here in the Basque Country, clinical fibrosis. In the case of these diseases, what we greatly benefit from is being able to study the entire genome, take a snapshot, and try to learn which mutation causes this disease and which gene justifies why these cases are necessary to activate genetic counseling.

So in these cases, we study the entire genome because we know we will have a mutation in a gene that explains these hereditary diseases. And then, in the other major branch of genomics, the research we are doing today, are the diseases called multifactorial, they are complex diseases with many genes associated with them. We have environmental factors, for example, diabetes, schizophrenia or asthma, which are much more complex.

And in the case of these diseases, what we are doing, also benefiting from the increase in the capacity to sequence the genome, is conducting studies of large cohorts,

Right: Taken from Pexels image bank.





where we have many people with disease and many people without disease, and we are comparing position by position of the genome, which is different between them, to try to learn which genes regulate these diseases.

So, I think it's good to make this distinction, because on one hand we have diseases, which is the classic genetics where we think that if we look at the genome we will discover a mutation, because it's very deterministic. And then we have studies or ways of investigating diseases that are more complex, where we already have to think about a genetics that is probabilistic.

What we need to understand is which positions in the genome give more or less risk of having a disease, even though not everyone with a mutation will end up developing those diseases like asthma or diabetes.

And one of the long-term goals is to advance towards precision medicine, right, adapting health treatments to individual profiles. This approach focuses on predicting the risk of diseases at an individual level.

Could you tell us how genomics is being used to develop tools that assess this risk and what challenges are faced on this path towards personalized medicine?

- Science takes time. We already have evidence that things are working and that it's being useful for studying people.

For purely genetic and deterministic diseases, like some found in newborns in the USA, doctors compare the genomes of sick infants and their parents to identify mutations.

Right, up: Urko Martínez Marigorta, below: podcast episode cover.

“And one of the long-term goals is to advance towards precision medicine, adapting health treatments to individual profiles, predicting the risk of diseases at an individual level.”

This method has helped diagnose and treat conditions in about one-third to one-half of cases, allowing tailored treatments that can save lives.

For complex diseases, we are moving towards precision medicine, which is challenging. Instead of deterministic risks, genetics often gives a probability of developing a disease. By analyzing a person's genome, we can calculate the likelihood of diseases like diabetes or asthma and make better-informed medical decisions. Although there are promising examples, like optimizing cholesterol treatments based on genetic risk, there are non-established programs yet to fully utilize this genetic information.

What is the role of lifestyle, and what data or methods do you use to investigate these gene-environment interactions, aside from our own genetics?

- From a geneticist's perspective, while lifestyle factors are very important, genetic differences between individuals also play a significant role. This means lifestyle affects each person differently. Besides genetics, we now consider the "exposome", which includes all environmental and lifestyle factors that influence disease development. Unlike genetics, where we've made significant technological advances, we lack the same capability to measure lifestyle

systematically. Devices like the Apple Watch are starting to change this, allowing us to systematically measure an individual's environment.

Over the past two decades, genomics hasn't fully incorporated the role of lifestyle despite its importance. Once we can systematically generate lifestyle data, we'll better understand how genetic variants interact with lifestyle, driving the increase in multifactorial diseases.

What advances are expected in the coming years, and how could they impact medicine and public health?

- It's like with all technologies, such as the internet: in three to five years, nothing seems to change, but after 20 years, you realize it has completely transformed your life. I believe genomics will follow a similar path. In the next two decades, we will see significant changes, especially in how we diagnose diseases. We're in a limbo where research shows great promise, but implementation is still uncertain, despite clear examples of its potential usefulness.

FROM GENES TO MAPS:

CARTOGRAPHY OF CANCER

Cancer, an adversary that confronts millions globally, remains one of the most challenging medical puzzles of our time. But what truly lies at the heart of this complex disease? To fathom its depths, we must navigate through its multifaceted layers, peering into the inner workings that govern its existence.

Imagine our cells as elaborate manuscripts, each one containing the blueprint of life encoded within its DNA. Over the course of our existence, this genetic code undergoes subtle alterations known as mutations. While some are benign and a natural consequence of aging, others hold the potential to unleash a cascade of events, ultimately culminating in cancer.

But amid this genetic variability, why do only certain mutations trigger the development of cancer? What interplay of factors dictates this outcome? And how do researchers navigate this intricate landscape of cellular complexity?

Join us on a journey as we embark on an exploration of cancer's enigmatic depths. We'll unravel its secrets, guided by the

expertise of **Isabel Mendizabal**, Ikerbasque Emerging Leader in the Cancer Cell Signaling And Metabolism research group at CIC bioGUNE. Through her work, we aim not only to comprehend cancer's molecular intricacies but also to pave the way for innovative treatments and preventative measures.

Most likely, we've all heard about cancer, a disease that is estimated to impact 1 in 2 men and 1 in 3 women today. But Isabel, could you please explain to us what cancer actually is?

- Well, cancer, rather than being just one disease, we could say that cancer is a group of diseases that share in common abnormal and uncontrolled growth of some cells in our bodies.

Our tissues are made up of millions of cells, and under normal conditions, these cells follow a fairly orderly life cycle. They are born, they divide, and then they move in a way that is already programmed. However, in cancer, what happens is that this process is disrupted, and the cells continue to divide and grow without any kind of control.

As a result, these cells end up forming masses of tissue that we call tumors. And in the case of cancer, which are malignant tumors, what we mean by this is that these cells are also capable of invading adjacent tissues or even spreading throughout the body through the bloodstream or lymphatic system. This is what we call metastasis.

And as for the causes, as mentioned in the introduction, we have known for decades now that cancer originates due to alterations in DNA, in the genetic material, which we normally call the genome, which is the set of genes in our cells. And these alterations, these mutations, can have three different origins.



Right: Taken from Pexels image bank.



On one hand, we know that exposure to mutagens, to agents that cause mutations, can change our DNA.

For example, we know about the case of tobacco smoke, for instance, in the case of lung cancer, or ultraviolet rays from the sun, which we have also heard about many times, affecting the incidence of skin cancer. But mutations can also be inherited; a predisposition to cancer can be inherited, or simply, as mentioned earlier, it can be due to inevitable errors in our cells that accumulate as we grow older. So, it is for this main reason that cancer appears mainly in older ages.

And from the perspective of cancer research, Isabel, how are the challenges in understanding this highly prevalent disease being addressed? What is currently being done?

- At CIC bioGUNE, we specialize in omics techniques, which have revolutionized biology and medicine. These methodologies allow us to study thousands of molecules simultaneously and systematically, providing comprehensive insights into tumors.

Recent advancements enable us to not only analyze the entire tumor but also profile each individual cell within it. This reveals the remarkable heterogeneity of tumors and sheds light on why some develop resistance to therapies.

Moreover, studying cells from healthy tissues has unveiled that mutations once thought exclusive to tumors are also present in healthy tissues. This challenges our understanding of cancer's origins and necessitates a broader perspective on its development.

Right, up: Isabel Mendizabal, below: podcast episode cover.

“In cancer research, omic techniques are already being used in clinical practice, which could improve early diagnosis and develop more personalized therapies.”

Understanding the diverse cellular composition within tumors, including immune and vascular cells, is key. It elucidates how cancer cells manipulate antitumor responses, offering valuable insights for developing more effective therapies.

This innovative research approach generates a vast amount of data that must be analyzed to draw conclusions. What are the highlighted advantages of this methodology?

- There has been a huge revolution in biology, which has given rise to a new discipline: bioinformatics. Now we need researchers with knowledge of biology, but also capable of analyzing large volumes of data and applying advanced statistics, programming, and computing to turn that data into interpretable information. However, one of the current challenges in biology is the gap between data generation and its transformation into useful information. This not only represents an analytical challenge but has also changed the way science is designed and conducted.

Previously, in biology, work was based on working hypotheses based on what was known or on previous research. Now, with bioinformatics, science is more data-driven, generating hypotheses as data is analyzed. This allows us to overcome biases

in knowledge and discover completely new processes that were not previously considered possible.

From your perspective, where do you believe research is heading, and how might it impact cancer prevention and treatment?

- In cancer research, omic techniques are already being used in clinical practice, which could improve early diagnosis and develop more personalized therapies. Furthermore, integrating these techniques with artificial intelligence and imaging could be key to detecting cancer at more treatable stages.

Regarding treatments, the discovery that tumors have multiple identities suggests that therapies may become more complex, possibly requiring combined approaches. Immunotherapy is also a promising area, harnessing the body's mechanisms to fight cancer. Although there is still much to understand, these advances promise to significantly transform cancer prevention and treatment in the coming years.

BEYOND THE PLATE:

CANCER AND NUTRITION

In the expansive landscape of human health, cancer emerges as a multifaceted challenge, casting a shadow of uncertainty over our understanding and treatment capabilities. At its core lies the tumor microenvironment, a dynamic realm where cancer cells engage in intricate interactions and dialogue with a myriad of other cellular players within our body, including the vigilant defenders of the immune system.

Simultaneously, the impact of diet on our overall health has become a subject of growing interest and intensive investigation. Within this realm of contemplation, we embark on a journey to unravel the linkages between nutritional choices and our susceptibility to cancer. Moreover, we dare to venture into the realm of therapeutic strategies, exploring how the food we consume might wield influence over the course of cancer treatment.

Yet, amidst our pursuit of understanding, we encounter a tapestry of unresolved queries. How do cancer cells navigate their path towards malignancy? What intricate mechanisms govern their unbridled

proliferation and invasive tendencies? And which specific dietary components hold the potential to sway these pivotal processes in cancer development and progression?

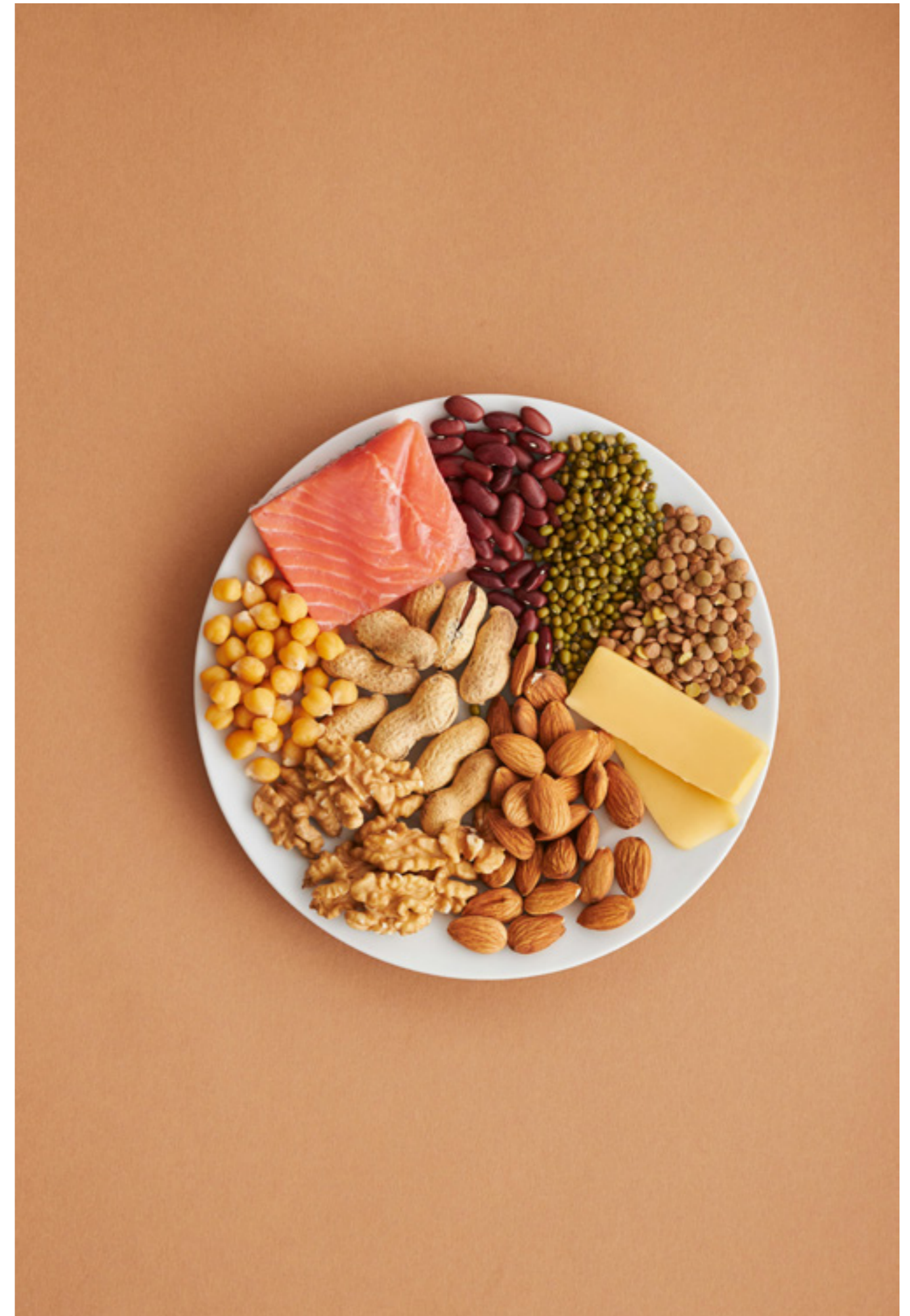
Guiding us through the maze of these compelling questions is **Arkaitz Carracedo**, Ikerbasque Professor and leader of the Cancer Cell Signaling and Metabolism group at CIC bioGUNE research center. With Dr. Carracedo's profound expertise and commitment to scientific excellence, we are poised to gain invaluable insights into the workings of cancer biology, illuminating pathways toward confronting this formidable adversary that impacts countless lives across the globe.

How does a cancer cell work and why is it so important to understand its functioning at the molecular and cellular level?

- Ultimately, our bodies and all living beings are composed of cells, these fundamental units. Since we are a single cell, we do nothing but divide and grow and grow in mass. We see it in little children, we see it when we get older. That entire process requires cells to copy its entire instruction book.

We have a copy of our father and a copy of our mother and although the cells do it very well, sometimes in that process of rewriting and making a new copy of the instruction book for the next cell, mistakes are made. When these mistakes are made, cells can change their functioning, they can stop understanding what their function is and acquire new functions. That's where cancer comes from, just as it comes from many other pathologies.

Right: Vanessa Loring, taken from Pexels image bank.





What elements of our diet can have an impact on the mechanisms of cancer development?

- As in the previous episode where you talked about the immune system and the entire microenvironment, here we must keep in mind that once we have a cell that begins to divide uncontrollably, with the aim of surviving, proliferating and generating more cells, everything around her can be used both to her benefit and to her detriment. Diet is our most direct interaction with the environment, therefore it will change the context in which that cancer cell is growing, for better or worse.

Therefore, it is an important factor because it is not only what we eat, but also how our body is balanced. People with diabetes not only eat more or less sugar, but also how they manage it.

The same thing happens with other types of diseases, therefore, it is something that is in our power and can be used, but it must also be used correctly. It is a double-edged sword. Many readers might be asking, "What is the diet we should follow?" Well, logically speaking, we have the Mediterranean diet at hand, right? And I think we all know a little bit about eating healthy, making it normal to eat healthy.

I'm not saying one day, because we eat something a little indulgent, but in general, we eat healthy. Yes. As we said before, just as diet is an important factor, the appearance of cancer is a process that occurs as a consequence of living.

Let's say that we simply live and grow old, we are going to have a certain chance of developing cancer. We're going to have, let me reiterate, we're going to bingo and we're going to have some cards.

Of course, depending on how we live and our lifestyle habits, we may have more cards or fewer cards.

But it will always be a matter of luck if it's our turn. What it means is that, if we smoke, if we do not protect ourselves from the sun, if our diet is not balanced, we are going to increase our chances. That does not mean that we are going to develop cancer, nor does it mean the opposite, that leading a super healthy life will keep us away from it.

It means that there are things that are under our control, and it is estimated that approximately a third of diagnosed cancers could be avoided by altering our lifestyle habits. And that includes tobacco, alcohol, sun exposure, certain viral infections, diet, etc. All of which can disrupt the environment we were talking about, leading to more complicated management of those cells.

And if we focus, for example, on treatment, how have these nutritional strategies been included in therapies against this disease?

Here we can speak at two levels. We can talk about how to use nutrition, our nutrition, in cancer treatment or we can talk about how you can use the nutrition of cancer cells, how cancer cells are fed to make better treatments. And it works in both directions.

“At the level of the tumor cells, knowing what mechanisms are used or how cancer cells are fed, we can translate that knowledge into drugs that allow us to better treat the disease.”

In the context of our diet, studies are being done on how specific diets or some modes of fasting, for example, combined with treatment can increase the effectiveness of treatments. But all this, and this is very important, in the ideal application of these strategies would always be as part of the treatment. That means under medical supervision in the context of what treatment is used.

That's why I said that diet is a double-edged sword. If we are being treated with chemotherapy and we also go on an extreme diet that instead of strengthening us weakens us, it still makes the chemotherapy feel worse for us. So all this has to be very well coordinated from a medical point of view to use diet as a tool.

And at the other level, at the level of the tumor cells, knowing what mechanisms are used or how cancer cells are fed, we can translate that knowledge into drugs that allow us to better treat the disease.

Right, up: Arkaitz Carracedo, below: podcast episode cover.



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



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**.



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BioEnredados

Uniendo Ciencia y Vida

First Season - Volume 2



A co-production of:

CICbioGUNE

MEMBER OF BASQUE RESEARCH
& TECHNOLOGY ALLIANCE



COPE

101.0 FM

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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?

BACK TO THE PAST

THE POWER OF GENE EDITING

Imagine a world where we could edit the fundamental building blocks of life as effortlessly as we revise a text document on our computers. What if correcting genetic errors could be as simple as fixing a typo? We journey into the fascinating and transformative realm of molecular biology to uncover a tool that is reshaping the future: CRISPR-Cas.

This groundbreaking genetic editing technology allows scientists to alter DNA with unparalleled precision, like fine-tuning the words in a digital manuscript. The implications of this technology are vast and profound, with the potential to correct genetic defects, treat incurable diseases, and even eradicate certain conditions before they manifest.

In recent years, CRISPR-Cas has emerged from the confines of the laboratory to become a beacon of hope for millions. Its approval for treating genetic diseases has sparked a wave of excitement and possibility, heralding a new era in medicine where the seemingly impossible becomes achievable. Diseases once deemed untreatable are

now within the realm of potential cure, offering a glimmer of hope to individuals and families affected by genetic disorders.

But how did we arrive at this revolutionary point? What is the science behind CRISPR-Cas, and how does it work? We will explore the origins and the mechanics of this extraordinary technology, shedding light on its current applications and future potential.

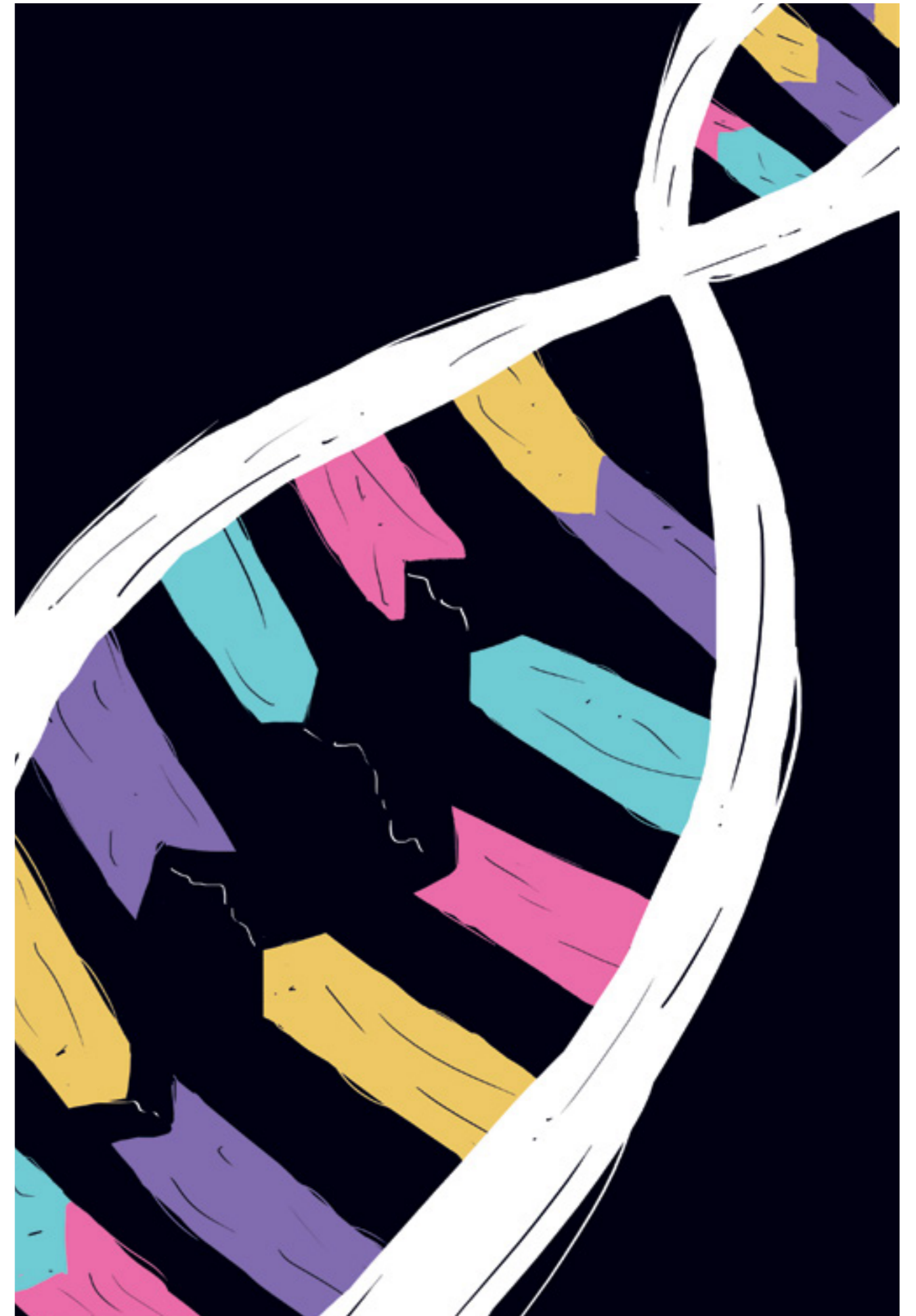
Our guide on this journey is **Ylenia Jabalera**, a postdoctoral researcher under the prestigious Juan de la Cierva program, who works in the Synthetic Biology Group at CIC bioGUNE. Ylenia's insights will take us through the historical roots of CRISPR-Cas, revealing how a discovery in bacterial defense mechanisms has evolved into one of the most powerful tools in genetic research and medicine.

Could you please elaborate on what the CRISPR-Cas genetic editing technique is and how it operates?

- It can be defined as a cut-and-paste or cut-and-rewrite tool at the molecular level. In nature, the CRISPR-Cas system serves as a bacterial adaptive immune system. Analogous to our antibodies, it memorizes genetic sequences of external invaders such as viruses. When the same virus invades again, this tool acts like molecular scissors guided by the system to cut the invader, preventing infection.

About a decade ago, scientists discovered they could apply this technology to genetic editing, sparking a scientific revolution. In fact, two researchers involved in this breakthrough were awarded the Nobel Prize in Chemistry in 2020, profoundly altering the field of molecular biology.

Right: Artistic interpretation by Ilargi Arakistain, student at Argi Arte. As part of the CIC bioART project.





Think of CRISPR-Cas as highly precise molecular scissors. To edit a gene, scientists design a guide RNA sequence that directs these molecular scissors to the exact location for cutting. Once they locate this region, the molecular scissors make a specific cut. Subsequently, cellular mechanisms take over, leading to different outcomes such as insertion, deletion, or rewriting of genetic material.

Therefore, we can use this tool to correct mutations associated with various pathologies.

What are the main applications of this technique in medicine, and what are some current examples of its use?

- Essentially, the primary application is genetic editing.

In fact, 2023 has been a pivotal year for this technology. In the last quarter of 2023, all major drug regulatory agencies, including the European, British, and American agencies, approved a medication called Casgevy. This drug, developed by Vertex and CRISPR Therapeutic, is based on CRISPR-Cas technology. It has been specifically approved for treating certain cases of two rare diseases: sickle cell anemia and thalassemia.

In simple terms, this therapy involves extracting the patient's hematopoietic stem cells. These cells are then modified in the laboratory using CRISPR-Cas tools to correct the mutation responsible for the disease. The edited cells are carefully screened to ensure they have been properly modified. Once confirmed, these edited cells are reintroduced into the patient, replacing the defective cells with the corrected ones.

Right, up: Ylenia Jabalera, below: podcast episode cover.

“Despite these challenges, ongoing research advancements suggest promising strides towards realizing the technology’s full therapeutic potential in the near future.”

You’ve provided us with a general overview of the technique and its applications online, but could you explain specifically how your research is contributing to the understanding and advancement of this technology?

- The CRISPR-Cas technology has immense potential in biology and medicine, but up to date, it is not perfect and faces several challenges. One of the primary issues is known as sequence recognition. Imagine these molecular scissors are highly precise and can make cuts, but to do so, they need to recognize a tag next to the sequence they are supposed to cut. Each scissor is specific to a particular tag. So, even if you can guide the molecular scissors to the target site, such as a mutation you want to correct, if the scissors do not find the tag, they will not be able to make the cut.

The current molecular scissors technology is limited by its need for specific tags to target mutations, restricting its application. To overcome this, our research group has turned to ancient times, resurrecting and characterizing ancestral scissors. These scissors are surprisingly flexible, recognizing multiple tags and thereby broadening the range of mutations that can be targeted. We are collaborating with the FUNDELA association to use these super-flexible ancestral scissors for treating Amyotrophic Lateral Sclerosis (ALS),

focusing on mutations in the SOD1 gene. Our preliminary results show potential, as these ancestral scissors can reach mutations that current technologies cannot.

What can we expect from the future of CRISPR-Cas?

- This technology holds immense promise for correcting and potentially curing genetic diseases at their core.

Despite its undeniable potential, we lack complete control over CRISPR-Cas technology. Current therapies involve complex ex vivo processes where cells are extracted, modified, verified, and reintroduced into patients. However, achieving in situ therapy—directly editing genes within the body—requires overcoming significant hurdles related to safety, efficacy, and precise targeting. Key obstacles include developing efficient delivery systems that can target CRISPR-Cas exclusively to desired cells or tissues without off-target effects. Despite these challenges, ongoing research advancements suggest promising strides towards realizing the technology’s full therapeutic potential in the near future.

GLYCANS

THE SWEET SIDE OF INFECTIONS

In the vast and complex landscape of cellular biology, glycans play a crucial role as essential molecules that contribute significantly to the composition of our bodies. Representing approximately 90% of the molecules found within us, glycans are chains of sugars, technically known as molecules with glycosidic bonds. These include compounds like polysaccharides and carbohydrates.

Glycans are predominantly located on the surfaces of cells, where they serve not only as structural elements but also as essential facilitators of cellular communication. Beyond their role in cellular communication, glycans also act as pivotal gateways for microscopic invaders like viruses and bacteria. These pathogens exploit glycans as entry points to infiltrate our cells. Once inside, they can hijack cellular mechanisms to reproduce and spread, leading to various infections and diseases.

Understanding the way glycans function as access keys for these pathogens is crucial for developing innovative strategies to combat infections. The study of how glycans enable

such invasions provides valuable insights that could lead to new preventive and therapeutic measures against many diseases.

Delving into the world of glycans leads us into the field of glycobiology, which focuses on the complex interactions between glycans and other molecules. But, what types of molecules do glycans interact with? How are these vital connections established and analyzed? What role do glycans play during the infection process when pathogens invade our bodies?

We seek answers to these fundamental questions with **Luca Unione**, Associate Principal Investigator in the Chemical Glycobiology Group at CIC bioGUNE. Luca's work explores the significant roles glycans play in health and disease.

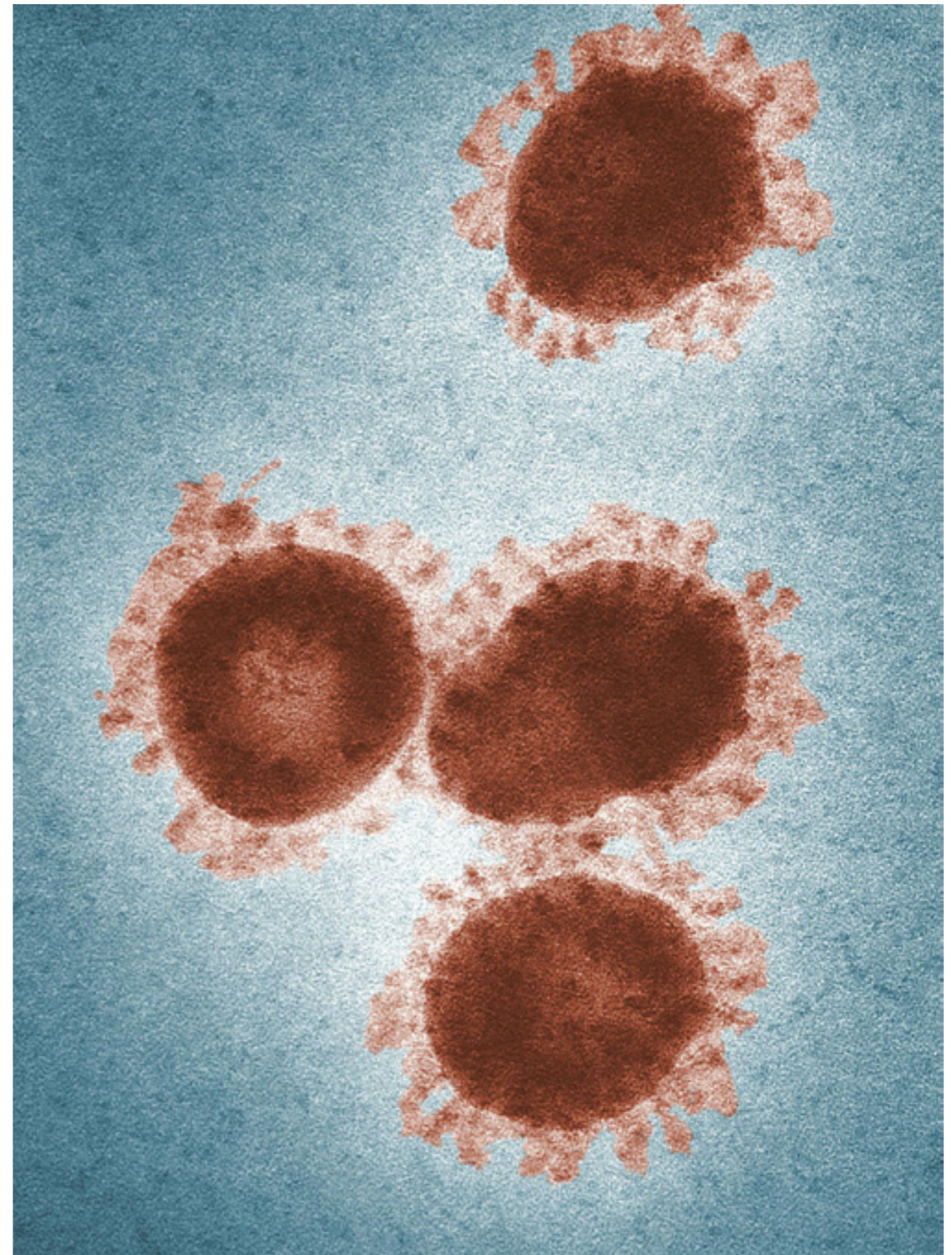
Let's now discover what glycobiology is exactly, and for that, Luca, the first question is: what exactly are glycans and what role do they play?

- When we talk about glycans we are referring to molecules, biological molecules that naturally occur in our body, and essentially we are talking about sugars.

These are the same molecules that constitute the sugar we add to coffee or tea in the morning. They simply form a diverse family containing various members, very similar to each other but different, consisting of small molecules that assemble to form highly complex structures. And what role do they play? Well, all our cells are covered by a layer of sugars, as you mentioned earlier, and there, on the cell surface, they play two fundamental roles.

The first is a structural and stability role, providing stability, structure, and presentation to the larger molecules they are attached to, such as proteins or lipids (fats).

Right: CDC, taken from Pexels image bank.





On the other hand, they play a crucial role as intermediaries for communication between cells and between cells and pathogens.

How can glycans interact with various molecules in the cellular environment? And what methods are used to study these complex connections?

- When we say they interact, it's because both other cells and pathogens have a series of proteins called glycan-binding proteins. These proteins recognize and bind to glycans on our cells, allowing cells to approach, communicate, and exchange signals. When the other entity is not a cell but a pathogen, these proteins facilitate not only binding but also fusion between these two entities, promoting colonization and infection.

To study these mechanisms, we now have various spectroscopic techniques that allow us to see the atomic details of this

interaction between these molecules.

With the context you've provided so far, Luca, could you explain more specifically how your research is contributing to advancing our understanding of this field of chemistry?

- Well, in this context where glycans are pivotal in virus infections, our research endeavors to unravel the precise mechanisms: which specific glycans facilitate the infection process and the exact proteins that orchestrate these interactions. Understanding these dynamics is crucial as it holds the key to potentially inhibiting viral infections, such as influenza, and other similar pathogens.

The significance of this research cannot be overstated. Viral infections, particularly those like influenza that have persisted for centuries, continue to pose significant challenges to public health worldwide.

By pinpointing the glycans and proteins involved, we aim to develop strategies that could disrupt the infection process at its core. This could lead to advancements in antiviral therapies and vaccines, offering new hope in the ongoing battle against infectious diseases.

What do you think could be the future applications of this knowledge and how could they impact our understanding and treatment of infectious diseases?

- There are more common viruses like the flu, for example, which remains a virus with high mortality in people with underlying conditions. But there are also recent viruses that have alarmed us, like coronavirus. Thanks to this type of research, we now know that glycans also play a crucial role in infection processes such as that of the coronavirus, enabling a structural change in the spike protein of the virus, which facilitates binding.

Therefore, by understanding how this mechanism takes place, we can develop potential drugs that can prevent this binding and thus protect ourselves. Some of these molecules are medications, small molecules, and to do this we need to identify accessible regions of the virus proteins, which we can then target with these small molecules.

Right, up: Luca Unione, below: podcast episode cover.

“We now know that glycans also play a crucial role in infection processes. If we can define specific glycans, we can also develop vaccines that are more effective against infection.”

On the other hand, this research also plays a crucial role in vaccine development. When pharmaceutical companies develop vaccines against infections, they enable our bodies to produce a harmless viral protein—not the entire virus—activating our immune system so it can recognize and fight the virus when encountered.

Glycans play a critical role in shaping the protein's structure. Identifying specific glycans could enhance vaccine efficacy against infections and detailed examination of how the virus attaches to and colonizes cells is essential for anticipating and preparing for future pandemics. Just remember that for the flu virus, throughout the last century, we have experienced four pandemics, and we know that sooner or later another one will come.

The virus constantly mutates, so the only way we have to predict the arrival of a new pandemic and be prepared to face them is to study in detail those mechanisms of attachment and colonization of the virus to our cells, and to develop potential medications.

BETWEEN AIR AND HEALTH:

THE VITAL ROLE OF OXYGEN

Oxygen, that essential yet imperceptible gas that surrounds us, is vital to our existence from the moment of our birth. Every cell in our body depends on it to carry out its most basic functions. However, have you ever wondered what happens when we lack this vital element? How does our body react to oxygen deficiency? In environments where oxygen concentration is low, such as in high altitudes or situations where access to sufficient oxygen is limited, our bodies face a critical challenge known as hypoxia.

Hypoxia occurs when cells do not receive adequate oxygen to function properly. This can have significant consequences for our health, as oxygen is crucial for cellular energy production and maintaining vital bodily processes. How does our body adapt to these adverse conditions? What mechanisms does it activate to ensure survival and function?

Moreover, understanding the connection between oxygen deficiency and the development of serious diseases such as cancer, cardiovascular and respiratory diseases, and anemia is

crucial. How does hypoxia influence these contexts? What role does it play in the progression of these diseases, and what research is being conducted to better understand this relationship?

To delve into these questions, we are joined by **Edurne Berra**, Associate Principal Investigator in the Signaling and Metabolism of Cancer Cells Group at CIC bioGUNE. Through her expertise and insights, we will explore how studying hypoxia can offer new perspectives for human health and the development of innovative medical treatments.

What is the role of oxygen in our body and how does it affect our health?

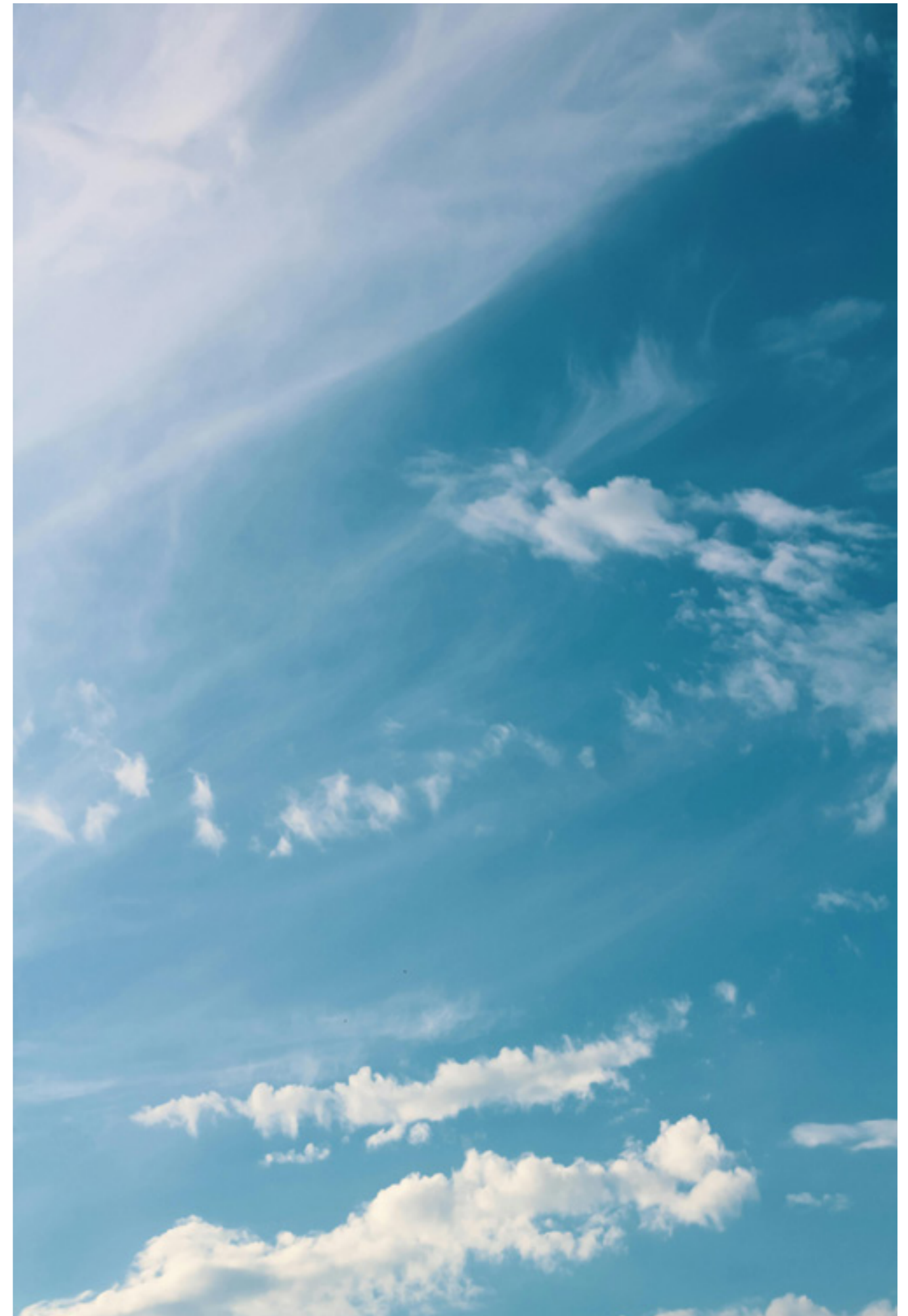
- As mentioned, oxygen is vital for each and every one of the billions of cells that make up our organs and tissues. We could say we are oxygen addicts. Oxygen is our energy source, which makes it incredibly important—it's like gasoline for a car.

We need oxygen to survive, but it's crucial that we have the right amount—not too much, not too little. Excess oxygen isn't beneficial, and as you pointed out, oxygen deficiency, or hypoxia, is even more dangerous. The good news is that our bodies are capable of reacting, adapting, and restoring necessary and appropriate oxygen levels.

Unfortunately, our body's response and adaptation aren't always as precise as we need them to be. Sometimes, our response is insufficient, while in other cases, it's excessive. In these instances, yes, hypoxia does affect our health.

Conditions such as anemia, stroke (like a stroke), heart attacks, and sleep apnea are all associated with inadequate adaptation to oxygen levels. On the other hand, some conditions, like cancer, for example, actually benefit from hypoxia.

Right: Taken from Pexels image bank.





What scientific advancements have been achieved in understanding these regulatory mechanisms of the diseases and what are their potential effects?

- Over the past 25 years, significant strides have been made in this field, achievements we can be proud of. Specifically, three major breakthroughs stand out. Firstly, scientists have identified the conductor, the mastermind orchestrating our adaptation to oxygen deprivation.

This conductor is HIF, the Hypoxia-Inducible Factor, a protein that oversees a highly intricate program with a dual purpose: when oxygen is scarce, it aims to increase its supply while simultaneously reducing its consumption. HIF plays a pivotal role in this process. Secondly, oxygen sensors have been pinpointed.

These sensors act as vigilant guardians, triggering alarms when oxygen levels

are insufficient. They communicate this crucial information through intermediaries to the conductor, HIF, thereby initiating the necessary responses.

Thirdly, Von Hippel-Lindau (VHL) protein has been discovered. This protein serves as an intermediary or actor in this intricate biochemical scenario. When VHL malfunctions, it can lead to conditions such as the Von Hippel-Lindau syndrome.

The scientists responsible for these groundbreaking discoveries were awarded the Nobel Prize in Physiology and Medicine in 2019, underscoring the significance of their findings. However, much remains to be uncovered in this fascinating field.

“Understanding the regulation point by different pathologies is crucial, as it can act differently in various cases. Indeed, we have two potential avenues for manipulating hypoxia.”

Now that we have this comprehensive overview of the research unfolding in this field, specifically, Edurne, could you please elaborate on what your research focuses on and how it is contributing to the advancement of this field?

- Our research can be summarized into three main areas. Firstly, we aim to unravel the remaining mysteries regarding the mechanisms of adaptation to hypoxia, which is our fundamental pillar of investigation.

Secondly, we investigate the role of hypoxia in a specific type of cancer, precisely prostate cancer, as we have mentioned before how cancer cells exploit and benefit from hypoxia.

Thirdly, we collaborate with two patient associations focused on Von Hippel-Lindau (VHL) syndrome: the Spanish VHL Alliance and the Basque Country Sendabide Patient Association.

Understanding the regulation point by different pathologies is crucial, as it can act differently in various cases, as mentioned earlier. Indeed, we have two potential avenues for manipulating hypoxia.

What do you think could be the future applications of this knowledge, or what prospects do you foresee in this field?

- First and foremost, I wouldn't want to raise false hopes, but it's true and important to acknowledge that there are medications available on the market today for treating anemia.

These medications target the oxygen sensors, the guardians we discussed earlier. Additionally, in the United States, a medication has been approved. Here in Europe, it is currently only used in clinical trials, but this medication targets the conductor we mentioned earlier, HIF, and is used to treat certain types of tumors.

I like to think that one day we will be able to improve the diagnosis and, above all, the quality of life of prostate cancer patients and those suffering from VHL syndrome thanks to our research and gene therapy project. However, let's remain humble and recognize that for now, it's essential to continue researching.

Right, up: Edurne Berra, below: podcast episode cover.

FROM NATURE TO VALUE:

THE POWER OF ENZYMES

Enzymes stand as indispensable agents driving numerous essential biochemical processes. These specialized proteins transcend their role as mere catalysts; they are the cornerstone of biochemical transformations that support the fundamental essence of life.

Enzymes operate with remarkable precision and efficiency, accelerating chemical reactions that would otherwise occur at impractically slow rates. They enable us to break down nutrients for energy, replicate genetic material, and repair cellular damage, all with exquisite specificity and control.

Beyond their fundamental roles within organisms, enzymes are increasingly recognized for their pivotal contributions across diverse industries and environmental contexts. From agricultural practices to the emerging fields of bioplastics and biofuels, enzymes catalyze transformations that hold profound implications for sustainable development.

By converting agricultural residues into biofuels or transforming non-biodegradable

plastics into eco-friendly alternatives, enzymes offer innovative solutions to pressing global challenges such as resource depletion and environmental pollution.

To delve deeper into the workings of enzymes, we will be joined by Dr. **Raúl Pérez Jiménez**, Principal Investigator at the Synthetic Biology Group at CIC bioGUNE. With his expertise, we will delve into how these intricate biochemical machines are shaping not just our understanding of biology, but also paving the way towards a more sustainable and resilient future for humanity.

What are enzymes and what is their primary function in these biological processes?

- *Enzymes are proteins. The simpler name is proteins, but their more complex designation is biological macromolecules that serve two main purposes. The first is to accelerate chemical reactions within biological systems that would otherwise occur at time intervals incompatible with biological processes.*

Additionally, they directly enable processes that wouldn't happen without their intervention, making them crucial for life's chemistry.

How are new enzymes with enhanced capabilities for specific applications being discovered and developed?

- *In biotechnology, enzymes are prized for their remarkable specificity in catalyzing chemical reactions efficiently. When adapted outside their natural biological environments, they require modifications to function optimally, addressing challenges like temperature and pH variations. Techniques from rational design to evolutionary methods are employed to tailor enzymes for diverse industrial and biomedical applications, including biofuel production*

Right: Taken from Pexels image bank.





including biofuel production and environmental sustainability efforts.

Enzymes' ability to facilitate complex reactions efficiently, while remaining environmentally friendly, underscores their immense value across industries. Their adaptation through advanced techniques ensures they can operate effectively beyond their natural biological settings, supporting innovation is crucial for sustainable development.

However, this is far from trivial because an enzyme is like a word composed of many letters. There are 20 different amino acids that can combine in complex ways. So, they are very complex "words" that cannot be modified in any way.

Each amino acid has a function and specific characteristics. Therefore, techniques ranging from informatics to evolutionary-based approaches must be applied to make

applied to make very specific modifications and successfully adapt the enzyme.

What are the advantages of using enzymes for processing biomaterials compared to other methods used today? And what are the unused residues that can be utilized?

- Well, the advantages are twofold.

On one hand, as I mentioned earlier, enzymes are extremely specific and efficient. They can target a biological process with great efficiency, accelerating the reaction significantly. On the other hand, they are environmentally friendly because they do not cause pollution.

In other words, they are biological macromolecules that, unlike other metallic catalysts or solvent-based methods involving organic solvents, have virtually no pollution capacity. So, we are killing two birds with one stone. On one hand, we make

processes much more efficient and selective, and on the other hand, we do not pollute.

So, enzymes are extremely interesting from a biological point of view. There are enzymes for almost any biological material. Depending on what you want to modify, you would look for a specific enzyme.

But there is considerable interest in utilizing biological waste materials, such as biomass from forest residues, for example, which contain a significant amount of cellulose, lignin, and hemicellulose. These are very interesting materials for industrial use. Additionally, there are other polymers, for instance, crustaceans have a very interesting polymer called chitin, which also has a range of emerging applications. All these polymers can be chemically modified, but this often introduces factors that are not entirely environmentally advisable.

Therefore, using enzymes offers a significant advantage, not only because they are highly selective as I mentioned, but also because we could modify these components very specifically and without harming the environment.

“Using enzymes offers a significant advantage, not only because they are highly selective, but also because we could modify them specifically and without harming the environment.”

What do you think are the future prospects in enzyme research and their applications in biological processes?

- Increasingly, biological processes are being integrated into industry. Unlike a few years ago, we now have in-depth knowledge and databases with millions of enzymes offering diverse solutions.

Over the past decade, advances in genomics and proteomics have provided a vast library of enzymes, enabling the modification of numerous industrial processes that use biomass and other biological components. The capabilities for enzyme modification have significantly improved due to bioinformatics and artificial intelligence, allowing for more precise predictions and adaptations.

In the near future, we will likely have enzymes to modify almost any industrial process imaginable, expanding their use in daily life and various industrial applications.

Right, up: Raúl Pérez-Jiménez, below: podcast episode cover.

THE SCIENCE OF:

BREAST CANCER

Breast cancer is a disease that has captured the attention worldwide due to its high incidence and the serious implications it has on the health of millions of people. Although commonly associated with women, this type of cancer also affects men, albeit to a lesser extent. It has become one of the most significant challenges in modern medicine and is one of the leading causes of mortality among women worldwide.

The incidence of breast cancer varies significantly between different regions and countries. However, in recent decades, an increase in incidence has been observed in developing countries, possibly due to lifestyle changes and environmental factors.

Breast cancer is characterized by the uncontrolled growth of cells in the breast tissue, leading to the formation of malignant tumors. This type of cancer can manifest in various forms and at different stages of life, presenting a wide variety of symptoms and development patterns. Factors such as genetics, lifestyle, and exposure to certain substances can influence the risk of developing the disease.

Despite significant advances in breast cancer research and treatment, many aspects of this disease remain a mystery. Early detection methods, such as mammography, have improved survival rates, but significant challenges remain, including variability in treatment responses and the emergence of resistance to conventional therapies.

But, what is currently known about breast cancer? Why do some cases develop resistance to therapies? And how could artificial intelligence revolutionize the detection, diagnosis, and treatment of breast cancer?

To delve into these questions, we are fortunate to have **Maria dM Vivanco**, Principal Investigator in the Cancer Heterogeneity Group at CIC bioGUNE. With her expertise and knowledge in the field, she will help us better understand these challenges and the advances that are changing the landscape of breast cancer treatment.

What is the present status of breast cancer incidence, and what is the impact of this disease?

- We can start with some figures because the incidence of breast cancer is still increasing today.

We know, for example, that worldwide, 2.3 million new cases were detected in just one year. In Europe, there were more than half a million cases, specifically 604,000. And if we consider Spain alone, there are more than 35,000 cases each year. In Euskadi, to give all the numbers, there are 637 cases annually.

These are numbers, but perhaps more interesting is realizing that today, breast cancer remains the most common cancer among women globally, and it also has the highest mortality rate.

Right: Anna Shvets, taken from Pexels image bank.





Nearly 96,000 women in Europe die from breast cancer annually.

Despite a slight decrease in mortality, incidence continues to increase. Most cases are diagnosed between the ages of 45 and 69, which is why screenings typically occur within this age range.

In Osakidetza, mammography is done every two years for women aged 50 to 69. However, 21% of cases detected before age 50 are not covered by these screenings. This impacts women significantly, not only in terms of health but also personally, psychologically, socially, and within their families.

In previous episodes, we introduced the concept of heterogeneity in a tumor. Could you explain what this concept entails and what its implications are?

- There are different types of heterogeneity and complexity.

There are differences between patients, as tumors in one patient may not be the same as in another, requiring different treatments and resulting in different prognoses. Additionally, there is heterogeneity even within the same patient.

For example, in a patient with metastasis, sequencing studies have shown that the original tumor in the breast is not the same as the one that appears in the lung, bone, or brain, due to mutations and changes. Another surprising finding in recent years is intratumoral heterogeneity, meaning that tumors are not homogeneous masses but contain diverse cells that behave differently.

Some of these are cancer stem cells, which have essential properties, especially self-renewal and differentiation. These cells are responsible for initiating the tumor and for resistance to therapy, making them a focus of our laboratory.

Right, up: Maria dM Vivanco, below: podcast episode cover.

“We know that not all molecules effective in the laboratory are FDA-approved. So, models that better mimic human microenvironments are crucial.”

We've mentioned many figures before, but not survival rates. Although incidence is increasing, approximately 30% of cases see tumor recurrence. Forty years ago, only 40% of women survived, but today, 84% survive for five years. However, considering the incidence and the long-term outlook, the 84% five-year survival rate is still not sufficient.

Building on your previous comments, the next question naturally follows: What role does research, especially the work done by your group, play in the fight against this disease?

- We focus on studying resistance. When a patient is diagnosed with a tumor, the doctor, along with their team of experts, prescribes a suitable treatment based on the tumor's characteristics. However, even if two women with similar tumors receive the same treatment, one might be cured while the other develops resistance. This occurs because, despite clinical similarities, tumors can differ at the molecular level.

To address this, we work on identifying biomarkers, proteins, or molecules that help distinguish tumors at higher risk of developing resistance. For example, we've found that elevated levels of the protein SOX2 are associated with increased risk. Now, we're seeking inhibitors to reduce the expression or activity of this protein.

Additionally, we study the tumor microenvironment, as obesity in postmenopausal patients is linked to a higher risk of breast cancer and therapy resistance. We aim to understand how the environment influences these risks. We also investigate healthy breast tissue to compare and better understand the changes occurring in tumors.

We've talked about what you are currently doing, but what are the future expectations in the fight against this disease?

- One of the most exciting transitions we're enthusiastic about is moving towards 3D studies that consider the microenvironment and co-cultures. It's not just about studying or focusing on what happens with one type of cell, but understanding how it interacts with others within the tumor, aiming to replicate the complexity and heterogeneity observed clinically, and to do so as accurately as possible in the lab.

We know that not all molecules effective in the lab are FDA-approved. So, models that better mimic human microenvironments are crucial.



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



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.

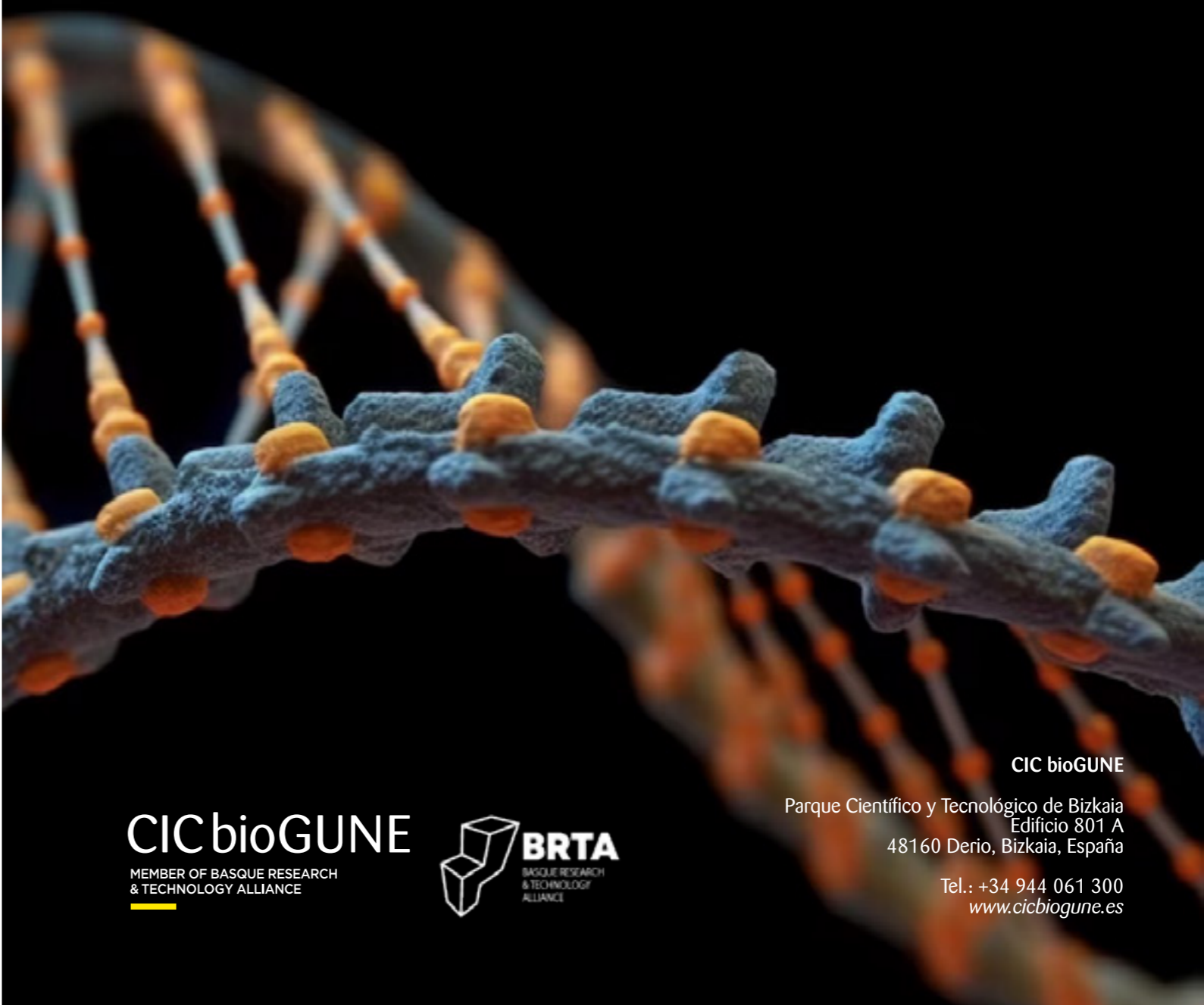
Recognized as a Severo Ochoa Center of Excellence, CIC bioGUNE leads cutting-edge research at the intersection of Biology, Chemistry, and Mathematics, focusing on Cancer, Rare Diseases, Infectious Diseases, and Metabolic Disorders. Our infrastructure includes advanced technological platforms that support 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**.



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