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biocat | Obra Social "la Caixa"

Synopsis

CANCER THERAPEUTIC RESISTANCE

PROGRESS AND PERSPECTIVES

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TREATING CANCER:
THE FIGHT AGAINST RESISTANCE

Cancer treatments are always progressing: in addition to diagnostic and surgical improvements, in recent years there has also been a whole battery of new drugs based on precision medicine, drugs that target the specific particularities of each tumor in each patient.

Nevertheless, a new obstacle has arisen in the fight. Tumors are able to evolve and adapt to the treatment, becoming resistant. In a way they behave like an infection trying to survive. To overcome this resistance, researchers are working on different approaches: analyzing the full genetics of tumors to better understand them and define better treatments, monitor their evolution and detect their weaknesses; at the same time, they are researching drug combinations to make it more difficult for tumors to escape their action; and for the past few years, they have been developing what is called oncology immunotherapy, the great hope in the fight against cancer in recent years, based on stimulating the body's own defenses to attack and control tumors. And all with sights set on the rising price of drugs, which threatens to make it difficult for the general public to afford them.

In order to present and discuss the latest advances, challenges and difficulties in the fight against cancer, national and international experts met for a B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate.

CONCLUSIONS

- Cancer treatments have improved prognosis in recent years, however the resistance tumors develop to treatments has been underestimated and is now the greatest obstacle facing the fight against cancer.
- Immunotherapy, which consists in stimulating our own defenses to fight tumors, is the great hope in oncology, and this is where much research is being focused.
- Large-scale genetic studies are allowing us to better understand the characteristics of each tumor and its weaknesses. The therapies of the future will be drug combinations to make it more difficult for tumors to escape their action.
- The increasing price of drugs is a growing problem. Some of the solutions involve better dialog between the industry and administrations, for example through what is known as results-based agreements (the hospital only pays the industry if the drug works).

RESISTANCE TO CANCER TREATMENTS: A PUBLIC HEALTH PROBLEM

"20 years ago, approximately half of all people diagnosed with cancer were still alive five years later. Now it's nearly 70%," explained Joaquín Arribas, director of the Preclinical Research Program at Vall d'Hebron Research Institute and one of the scientific leaders of this B·Debate. About 20 years ago, we also started using cancer drugs based on precision medicine: instead of destroying all the cells that divide, like classical chemotherapy, they target specific, highly altered cells in a tumor. This tends to make them more effective and with fewer side effects. Since then, most cancer drugs have been based on this philosophy, "Of the 45 drugs approved between 2009 and 2014, nearly all are based on pharmacological targets," said Arribas.

Nevertheless, **except in very few cases, the vast majority of these drugs end up failing**. Tumors act like living communities that evolve extremely quickly, like an infection. Some of them are indifferent to treatment from the very beginning. Others evolve to find a way out: they accumulate various changes in their cells aimed at helping them survive, and in many cases they do. This is why early diagnosis is important, so that surgery (alone or in combination with radiotherapy and pharmacotherapy) can get rid of all of the cells before they have a chance to evolve.

Miquel Àngel Pujana, researcher at the Catalan Institute of Oncology (ICO, IDIBELL) and co-scientific leader of this B·Debate, explained the problem in figures, "In 2015, the ICO diagnosed 1,700 women with breast cancer and 300 cases of resistance to treatment, which has a huge impact in terms of health but also on an economic level: **50% of pharmaceutical spending for breast cancer goes to treating resistances."** With this motivation, ICO and IDIBELL decided to create the ProCURE program (Program Against Cancer Therapeutic Resistance), which encompasses nine research groups all fighting this problem and is led by Pujana.

Faced with this problem, the question arises: Did we overestimate the ability of precision medicine? Arribas doesn't think so. For example, treatments of this kind have made certain types of leukemia a chronic condition, and for some breast tumors, "We now have four lines of treatment that be used, when a few years ago we couldn't do anything," he said. What happened is that "We underestimated the problem because we didn't understand it."

Now this issue is fundamental, and there are many approaches being studied to better understand and minimize it. One of these is understanding tumor genetics and evolution so we can stimulate the immune system to fight cancer.

TUMOR EVOLUTION AND GENETIC SIGNATURES

As a tumor cell divides, its daughter cells accumulate mutations that may differ from the original cell. In the end, this leads to a more or less heterogeneous conglomerate whose variability will establish how sensitive the cells are to treatment and even if they can resist it and reemerge after what initially appears to have been successful treatment.

In 2011, the group led by Elaine Mardis, professor of Genetics and Medicine at the Washington University School of Medicine, participated in the **first full genetic sequencing of a case of leukemia over time**. Their study proved which cells responded to treatment and which ones didn't. Now their studies are even more ambitious. "For acute myeloid leukemia there are very few markers that indicate a patient's prognosis, beyond whether or not they respond well to chemotherapy. Genomics can help improve that," explained Mardis. This is why they have studied the genetic profile of tumors in more than 70 leukemia patients. What they've seen is that if after one month there are at least 5% of cells with specific mutations, the patient's prognosis is much worse. This helps classify patients to know if they need new treatment before the tumor reappears.

The rise of genetic sequencing techniques and IT tools is gradually contributing **large amounts of information on tumors**. Cancer isn't one single disease, there are at least 200 different types and **really there are as many tumors as there are patients**. But some are more similar than others, thus the need to group them together because in theory each group should respond better to one treatment or another. One example of these analyses was done with colon cancer: the group led by Rodrigo Dienstmann, oncologist and director of the Oncology Data Science (ODysSey) Group at the Vall d'Hebron Institute of Oncology, has studied the large-scale genetics of more than 4,000 of these tumors and has established 4 different groups, with the specific characteristics of each one and a different prognosis after treatment.

Another way of grouping them is by looking for signatures of a few genes whose alterations determine their aggressiveness and, on occasion, their response to specific drugs. For colon cancer, several of these signatures are named after Ramón Salazar, head of Medical Oncology at the ICO.

But in some cases analyzing the tumor isn't enough, **its microenvironment must also be studied**, the tissue surrounding it and on which it sits. Eduard Batlle, coordinator of the Oncology Program at the Institute for Research in Biomedicine Barcelona, discussed this, saying that at least for colon cancer, "A tumor's tendency to metastasize depends not so much on the cancer itself but more on the tissue on which it is found." What they've seen is that most of the genes that predict a relapse are active at the microenvironment of the cancer, and that the vast majority are activated by a molecule called TGF-β. This is why scientists are working on drugs to inhibit it.

CANCER MODELS

In order to study new therapies, clinical trials are key. But before a drug can be tested on patients, it must be researched as much as possible in the laboratory.

One of the first ways of analyzing how a therapy works and behaves is to test it in cell lines, cultures on slides of immortalized tumor cells. But this is just the first step, far from the clinical reality.

In order to get a bit closer to the "real world", scientists then use models called "xenografts": **fragments of tumors from patients that are put in lab mice**. These models are widely used, for example, by the group led by Carlos Caldas, professor of Oncology at the University of Cambridge. Using large collections of these models, they've studied many characteristics of several tumors: their mutations, epigenetics, heterogeneity. And they're also looking for new drugs and combinations that effectively target specific mutations.

One step further is what is known as Orthoxenografts, a model made from **implanting a tumor fragment from a patient into the corresponding organ of the mouse**, thus closely reproducing the biology. One of the top experts in this model is Alberto Villanueva, head of the ICO Chemoresistance group and co-founder of the spin-off Xenopat, which generates these models. By using them, scientists can not only research the effect different drugs have on specific tumors, they can also reproduce the clinical progress of a specific patient. Implanting a tumor fragment in a series of mice can allow scientists to test various treatments at the same time to identify the most effective option.

CANCER IMMUNOTHERAY: THE GREAT HOPE

Although the role our defenses play in the fight against cancer has been known since the late 19th century, it has only been in the last five years that immunotherapy has become the great hope for cancer.

Our immune system is always on the lookout for foreign bodies. When a tumor begins, its mutations make it different from the rest of our cells and our defenses fight to eliminate it. But at some point the body can fail, because the cancer looks for ways to avoid its defenses.

One of these ways is to **cover itself in a sort of invisibility cloak**. Tumors do this with a layer of molecules called PD-L1. When these molecules interact with the complementary ones in the defense system's lymphocytes, they render them inactive. One of the most promising drugs is what is known as immune checkpoint inhibitors: antibodies that stop the tumor from being able to do

this. They have been particularly effective in treating melanoma (the most aggressive type of skin cancer), and they also seem to have an effect on tumors like those in the lungs and kidneys. In large part due to this, **cancer immunotherapy was named the scientific breakthrough of the year by the journal Science in 2013**.

But there are other types of tumors that don't seem to respond, and no one really knows why. The group led by Michael Karin, professor of Microbiology at the University of California, is studying possible reasons in prostate, liver and pancreatic tumors. "The immune system fights the cancer and some types of chemotherapy can help the body recognize it," said Karin. This theory is based in part on the fact that chemotherapy kills many tumor cells and, in destroying them, causes many of their substances to be liberated, making it easier for the body's defenses to *find them*. However, on occasion something paradoxical happens. As Karin explained, "It sounds unbelievable, but some B lymphocytes (the ones that produce antibodies) can inhibit the war the T lymphocytes (the ones responsible for coordinating the immune response) wage on the tumor after chemotherapy." These *rebel* lymphocytes seem to act through the PD-L1 molecule (the invisibility cloak), so "A combination of chemotherapy and immunotherapy, if administered at the same time, could be helpful for this type of tumor," he explained.

Another way of stimulating the immune system against cancer is through vaccines. Although they have shown promise for years now, only one has been approved for prostate cancer and its effectiveness is quite limited. But there are new strategies that seek to increase their power exponentially by designing fully personalized vaccines based on looking for the mutations in each tumor and determining which have the greatest probability of provoking a strong reaction from the defense system. This is the focus of the work of the group led by Sebastian Kreiter, director of the Immune Therapy Development Center (TRON) at Johannes Gutenberg University in Mainz, and their research has already led to a clinical trail on a personalized vaccine in melanoma patients.

And there is still another path in the approach to chemotherapy, which involves **using oncolytic viruses**. These viruses are harmless and selectively attack tumor cells. This is what the group led by Ramón Alemany, head of the ICO Virotherapy Center, is working on. "We want to fight tumors with viruses, but for the virus to also facilitate the work of the immune system," said Alemany. It would be somewhat similar to the role of chemotherapy, which in destroying the tumor cells *reveals* them to the defense system. But it isn't easy, because in many cases the viruses don't arrive in the right quantities and because the defense system tends to attack the virus more than the tumor itself. That's why scientists are working on solutions. Some of them include incubating special forms of viruses that can hide from the immune system or inserting part of the tumor into the outer coating of the virus so the body's defenses will attack both at once.

One way or another, the future seems to lie in good part down the path of immunotherapy, although not exclusively. Joaquín Arribas explained, "In many cases, cancer treatment will surely require a combination of immunotherapy and precision medicine with molecular targets."

ROUND TABLE:
STAKEHOLDERS IN THE FIGHT AGAINST CANCER IN THERAPY RESISTANCE

In the fight against cancer, scientific breakthroughs are essential. But so are political decisions and the economic cost of treatment. This B·Debate included a round table discussing the problems that new therapies and resistance generate in terms of the healthcare system. The discussion was moderated by journalist Josep Corbella and featured various stakeholders from the administration, patients' associations, industry and research.

According to Nieves Mijimolle, a member of the Spanish Association Against Cancer (AECC), "Patients live with the disease, but they also live in this world, and treatment has suffered with the recession." Treatments are increasingly expensive, given their complex development and production process. According to Francesc Mitjans, a member of the CataloniaBio association of businesses, "**Each cancer drug costs on average €1 billion**." Researcher Alberto Villanueva commented on that figure, among other things because it includes "the money spent on other drugs that didn't work." Villanueva was critical of part of the research done, mainly due to lack of industry interest, as much more research is being done into resistance to new drugs, although they are hardly used, "when we don't yet know the resistance mechanisms to much older drugs, which are the ones being administered today" (and for which patents have already expired).

One of main criticisms of the current research system in Spain is that innovation hasn't been developed sufficiently. For Victoria Ureña, deputy director general for Research on Cellular Therapy and Regenerative Medicine at the Institute of Health Carlos III, "**In Spain research has always been heroic. And innovation is Kafkaesque**."

But beyond that problem, how do we make sure constantly rising drug prices don't have a negative impact on patients? Both Nieves Mijimole and Gabriel Capellà, head of the Government of Catalonia Ministry of Health Innovation Program, believe that one way to improve would be the increasingly common **results-based agreements**, under which the hospital only pays the industry if the drug works. According to Francesc Mitjans, although "drug development is increasingly expensive, there is a possibility for dialog."