B·DEBATE International Center for Scientific Debate BARCELONA

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Synopsis

IMAGING FOR LIFE

FROM MOLECULES TO DIAGNOSTICS AND THERAPY

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Molecular imaging techniques for precision medicine

More and more, medicine strives for a greater level of precision. Identifying the exact process in each patient for the most precise diagnosis and treatment possible. It seeks to be more efficient and reduce side effects. And it has an increasingly important ally: imaging techniques. Techniques that have evolved from x-rays and MRIs to the latest tools that provide much more specific images, sometimes on a molecular level.

The latest techniques use fluorescence, nanotechnology and intimate knowledge of biology to assess specific drug actions, tumor behavior, or to help surgeons guide and delimit their operations. Use of these techniques on their own or in combination promises to be useful in research, but also in diagnosing and treating diseases. This capacity has given rise to the concept of "theranostics", the combination of diagnosis and treatment in one process.

In order to discuss some of the most recent and important advances, several of the top experts in the world came together on 8 and 9 November for the debate 'Imaging for Life. From Molecules to Diagnostics and Therapy' organized by B·Debate –an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate- in conjunction with the Institut de Biotecnologia i Biomedicina (IBB) – Autonomous University of Barcelona (UAB) and the Jožef Stefan Institute (IJS) - Ljubljana University (Slovenia).

CONCLUSIONS

- From x-rays, imaging techniques have evolved a lot in medicine. They now strive to be more specific and serve as a guide for what is known as molecular medicine.
- Most drugs fail in the final stages of development. Better visualizing how they work would help improve their efficacy.
- The new imaging techniques cover many medical processes. A new concept has been created, "theranostics", in which they are used simultaneously for diagnosis and treatment.
- Cancer is one of the diseases for which imaging is most important. New techniques seek to be useful for diagnosis, prognosis and even guiding surgeons during operations.

1. FROM IMAGING TECHNIQUES TO MOLECULAR MEDICINE

In 1949, chemist Linus Pauling and his team published a seminal study, establishing that a certain type of anemia was caused by specific alterations in the hemoglobin. This was the first time an abnormal protein was directly tied to a disease, meaning it was the beginning of what is now known as **molecular medicine**.

Nowadays this concept is commonplace, but scientists are still working to perfect it. According to Markus Rudin, professor at the University of Zurich, "In order to improve it, we need molecular diagnostic tools, and some of them have to do with molecular imaging."

The first widespread imaging technique was the **x-ray**. After that came **ultrasounds**, **MRIs**, tomography and, most recently, **PET** (positron emission tomography). This last technique uses positrons emitted by a specific compound to locate, for example, cancerous areas based on their higher glucose consumption.

Precision and differentiation increase progressively, but little by little research is being done with new techniques that provide an even more concrete, much more specific image. For example, **fluorescence** is being used in combination with selective molecules to identify and observe specific molecular targets. Computer models are designed to **recreate three-dimensional structures from flat images** and tools are being developed using **nanotechnology** to identify the properties of a single cell within a cell conglomerate.

The applications of these techniques can be used in many different fields. One in which quite a lot of work is being done is cancer, but they would also be useful in improving some aspects of Alzheimer's. For example, diagnosis of this disease is currently confirmed with a PET scan. Although, as Rubin explained, "That doesn't work for prognosis. We're working on different types of technology to observe both metabolism and inflammation, which have a better correlation with the progress of the disease."

Rubin's team is working on brain imaging techniques, in their case using mice. "**We're in the brain decade**," he said. "There are huge projects in Europe, the United States and Korea that are all trying to explain how it works." In his case, the use of animals in research is justified for several reasons: they serve as a model of the disease, their neurotransmitters work in a similar way to those of humans, and they can fine-tune the results from functional magnetic resonance imaging. In this case, it is assumed that the increase in blood flow the technique captures shows that this region is working. But this correspondence isn't necessarily mathematical and unequivocal. "Animal studies allow us to look at this relationship," explained Rubin.

Another area in which imaging is gaining importance is drug research.

In computer science, according to Moore's law, the number of transistors in a processor doubles every two years. "**Unfortunately, drug development doesn't follow this law**," said Oliver Plettenburg, director of the Institute of Medicinal Chemistry in Munich. In fact, "The number of drugs developed is decreasing, as is the amount of money invested. In 2016, only 19 were approved."

The majority tend to fail in the final stages of development, in general due to lack of efficacy when tested in clinical trials, despite having shown promise in the laboratory. "**We don't understand the illness enough, or we underestimate the heterogeneity of patients**," said Plettenburg.

"Greater visibility of drug action in the early stages could help weed out ineffective drugs, or understand who they would benefit. For example, for patients with diabetes or atherosclerosis certain drugs may only be useful in specific stages of the disease."

There are several techniques being developed to improve drug research. For example, work is being done on methods to show how they occupy their targets inside the cell. "This would allow us to assess the efficacy and side effects, adjust the dosage depending on the fraction of receptors occupied at any time." **Work is also being done to monitor chemical reactions, with fluorescent molecules given off that can be seen as the reaction occurs**.

Some of these reactions are those carried out by what is known as **cathepsins**, proteins that destroy other proteins. Their function is important in pharmacology, as they are responsible for activating some drugs. But they are also essential to the cell: they participate in immune response, inflammation and even the creation of blood vessels. Changes in how they work can be seen in numerous diseases. One of these is cancer, where they can be key in the spread and metastasis of the diseases, by "breaking" the tissue surrounding it and allowing it to spread.

Visualizing and modifying cathepsins is the focus of the working group led by Boris Turk, professor of Biochemistry at the University of Ljubljana and one of the leaders of this B·Debate with Francesc Xavier Avilés, professor and group leader at the Autonomous University of Barcelona and the Institut de Biotecnologia i Biomedicina. The focus of Turk's work is twofold. On one hand, they are locating excess cathepsin activity using fluorescent molecules. On the other, they also incorporate a photosensitizer, a molecule that makes the cell sensitive and susceptible to light. **This allows them to combine**

diagnosis and treatment, locating the tumor and treating it specifically all with the same tool. It is what has been called "theranostics", and it is one of the approaches to cancer currently being studied.

2. IMAGING CANCER TO FIGHT IT

The fight against cancer targets different stages: precise early diagnosis, proper prognosis and, of course, effective treatment. Imaging techniques play a part in each of these stages, and researchers are studying how to perfect their use in each one.

The combination of **PET and CT techniques is one of the best tools** to diagnose and measure the size of a tumor. It generally involves using a specific marker to see cell populations that consume large quantities of glucose, as cancer cells have a faster metabolism. Work is also being done to differentiate them, to see the heterogeneity of the tumor. As Markus Rudin explained, some of these studies are focusing on how to identify and visualize cells with hormone receptors inside breast cancer, so they can be treated with blocker drugs. This way, **fluorescent techniques can be used to get a map of the initial composition and progress of the tumor over the course of treatment**.

The team led by Francisca Mulero, head of the Molecular Imaging Unit at the Spanish National Cancer Research Center (CNIO) in Madrid, is working on better prognosis techniques that can also guide personalized medicine treatments. To do so, they are studying **hypoxia: to what extent tumors lack oxygen**. These tumors normally grow in an unstructured manner, and even though they may also form in blood vessels, they are normally not enough to provide the oxygen levels needed. Cancer can adapt to any scarcity, which also allows it to resist certain treatments: radiotherapy is less effective and it is harder for chemotherapy drugs to reach them.

By perfecting techniques that combine PET and CT scans with a specific marker, **their work helps visualize and quantify the level of hypoxia in a tumor**. This has allowed them to assess the efficacy of new breast cancer drugs that seek to normalize blood vessels and therefore improve the effects of chemotherapy. What they've seen is that if the oxygen levels in the tumor fall below a certain level, the new drugs are ineffective. This could help guide their use, excluding patients who won't benefit from them.

Imaging techniques can also be used directly in treating tumors. For example, one of the most active areas of research is **cancer stem cells**, a small cell population that seems to be responsible for initiating metastasis and resisting therapies. The team led by Simo Schwartz –director of Nanomedicine at the Vall d'Hebron Research Institute in Barcelona– is working with nanomedicines that specifically target this type of cells. They use specific fluorescent markers for stem cells. This allows them to demonstrate their efficacy and behavior within the cell chaos of a tumor.

Imaging techniques are now reaching fields even more directly as treatments used every day, in surgery for example. This was explained by Quyen T. Nguyen, associate professor at the University of California San Diego, because "**knowing exactly where a tumor begins and ends is really hard**," she explained. In operations to remove a tumor, several samples are often sent to the pathologist to identify as quickly as possible whether there are still cancerous cells around those that have been eliminated. This implies that the excision is almost surely incomplete.

"This makes surgery more complicate and costly," said Nguyen. Her team has developed fluorescent markers that target proteins that are commonly found in tumors, which can then be seen during the operation. But not only that. They are also working on tools to "light up" and observe the nerves in order to help surgeons and decrease the possible side effects.

The organizers didn't hesitate in saying that "a picture is worth more than a thousand words." Obviously, it's hard not to agree with them.