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Targeted therapies

by Professor Gilles Salles

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He heads the "Indolent B Proliferation" research team which is devoted to studying the mechanisms explaining the occurrence of lymphomas, a fairly frequent cancer of the ganglions.

"The Synergie Lyon Cancer Foundation" is structured around clearly defined programs, with a project on cancer escape and a project on therapeutic targeting that consists in joining efforts to develop new tools to combat cancer.
The first treatments against cancer have been quite empirical:

- surgery to remove the tumor,
- perfusion chemotherapy to destroy most of the cells that divide,
- radiotherapy, which follows the same idea, but more focalized.

When, in the 1990s, we started to better understand why cells became cancerous, a certain number of potential targets in cancerous cells were identified for interventions.

These targets range from the selection of proteins expressed on the surface of a cancerous cell and that will be targeted by antibodies directed against them, to more complex mechanisms that regulate the major cellular functions that can be modified in certain types of cancer.

The idea today is to develop drugs that are not bulldozers, but that are based on a precise rationale which is "the specific anomalies present in cancerous cells".
Several hundred drugs have resulted from targeted therapies developed in the framework of clinical tests around the world and in healthcare centers in Lyon, such as the Hospices Civils de Lyon (HCL) and the Léon Bérard Center (CLB). However, they are effectively used in patients whose cancer is rather more advanced and patients would sometimes like to benefit from these treatments earlier.

Nonetheless, once a drug demonstrates its efficacy and sufficient tolerance in the patients whose cancers are advanced, we develop what is called clinical research. The drug concerned is positioned in the therapeutic arsenal alone or in combination with other drugs like chemotherapy. Generally, when a drug is efficacious and well tolerated, it is introduced quite quickly, that's to say in only a few years, and then used in the therapeutic arsenal used from the outset. However, in the eyes of the patient it's never quickly enough and it's understandable.
Care must be taken to conform to this algorithm of development for the molecules that are being developed now. Patients cannot be exposed to a new molecule while well codified treatments exist already which also provide results.

In the area of **hematology** (blood diseases), which is the area to which I devote my attention, three main examples of therapeutic targeted can be mentioned.

The first two are major discoveries since they make up the first two examples of targeting.
One of them is the targeting of what we call a basic mechanism of oncogenesis.
This is the example of chronic myeloid leukemia. It has been known since the beginning of the 1960s that the disease was characterized by chromosomal rearrangement, and that this led to the junction of two genes and thus the creation of an abnormal protein. Then we saw at the beginning of the 2000s drugs known as tyrosine kinase inhibitors capable of combating this abnormal protein in quite a specific way.
This has completely transformed both the lives of patients, who can take a drug orally daily (in comparison to the formerly cumbersome injections) and, above all, this disease, which was, unfortunately, always fatal. Now it has become a chronic illness. Admittedly, we cannot cure it, but many patients now enjoy a normal quality of life by taking this drug.

The second example is what we call **monoclonal antibodies** which target a specific protein located at the surface of cancerous cells.
The anti-CD20 antibodies represent a major breakthrough in treating lymphomas since they make it possible to cure substantially more patients.

The third example is topical since it is the subject of an article published in June 2013.
It's the example of a protein located on the membrane of B lymphocytes, from which lymphomas develop. This protein is called Bruton tyrosine kinase (BTK). BTK inhibitors have been developed with extremely impressive clinical results in diseases with very specific aggressiveness characteristics that were capable of resisting several treatments.

So we have specific drugs that target the anomaly of cancerous cells well and which permit very considerable therapeutic advances."