Towards a More Effective Anticancer Therapy

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To explore new frontiers in the quest to improve the quality of life of cancer patients. That represents the main focus of the research agenda of Doctor Belinda Pastrana-Ríos.

"We've all had a family member or friend diagnosed with cancer. Sometimes these patients are children and we would not want this illness to continue," that's the way the researcher describes the force that has motivated her to conduct studies in the field of cancer for the past ten years.

Although there are many treatments for this disease, science is still exploring other methods that might be more effective. Indeed, Pastrana-Ríos operates three laboratories in the Department of Chemistry, University of Puerto Rico at Mayagüez (UPRM) whose primary mission is to explore a solution based on the study of interactions between proteins.

"We know that what causes this condition called cancer relies in one or two mutations of a gene. Genetic therapies have proven to be very premature and have not been very effective. The next effort is to understand the interaction between proteins," said the professor.

According to the researcher who specializes in chemistry, when mutations occur in a gene, and these affect a protein, alterations that cause cancer occur at the cellular level. She added that this condition occurs when there is an uncontrolled cell division.

"Our effort is channeled to study proteins that are involved in cell division and

how they interact with each other. These studies will help us answer questions such as: What types of chemical interactions exist between two proteins? What changes occur in proteins when they interact with each other? One way to prevent cancer from multiplying is to avoid cancer cells from dividing. Our goal is to achieve the interruption or inhibition of interactions between proteins necessary for cancer cell division," she said.

With that purpose, the investigative phase began in 1997 at the Biotechnology Laboratory. From there, they began the task of "expressing" proteins using a fermenter that enables the growth of cell cultures as well as mutating and purifying the proteins. In fact, at that time they originated studies with a protein called *Centrin* from a unicellular dinoflagelated alga known as *Chlamydomonas reinhardtii*.

The initiative was expanded with the establishment of the first Center for Molecular Modeling and Visualization in Puerto Rico in 1988. According to Pastrana-Ríos, one of the advantages of this visualization system is that the proteins can be observed in three dimensions. It also allows one to create different representations of one or more proteins and see how they interact. These interactions produce all the cellular events and conditions of certain diseases, including cancer.

She explained that later, in 2002, she joined her efforts with the Protein Spectroscopy Laboratory. This scientific facility has two sophisticated instruments based on infrared technology. "We are the first in the world to work with a two-dimensional infrared technique for the study of interactions between proteins. The two-dimensional correlation technique is extremely sensitive to study and decipher the interaction between proteins," she said.

She added that the combination of techniques designed to generate mutation in a

protein, its purification, its infrared analysis, the determination of its structure and eventually its modeling are unique and new in Puerto Rico.

A More Effective Therapy

Through a combination of studies being performed in these three laboratories, which are located in the Chemistry building at the UPRM, we aim to achieve "a more effective anticancer therapy", she explained.

"We are involved in multiple efforts to identify ways to cause cell death to a cancer cell. This would be an alternative to the therapies that are currently used," she said.

One of the advances of the research process during these 10 years is that they began studying algae protein and since 2004 they have integrated the analysis of several human proteins Sfi1p, Centrin and their mutations.

Indeed, the scientist hopes that in five to seven years they may have a clinical application of this research. "If we can prove that these mutations are what we have conceptualized in our imaginations, they can directly bring some clinical applications. Although we do not like to think a lot in terms of time, because many variables can arise, we have already succeeded in generating and purifying the mutated protein. We are now in the process of generating and expressing the complex", she said.

How would that possible therapy work? asked **Sin Límites** to the professor. She assured that the important thing is to prevent uncontrolled cell division. "If I prevent cells from dividing it doesn't matter what happens in terms of mutation or cancer. The tumor can't grow and we can be sure of having the optimal solution at the clinical level: a localized tumor can be treated either by surgery, radiotherapy or chemotherapy."

She added that the way this therapy could be applied clinically would be through the use of a small molecule that is directed to disrupt the interactions between proteins involved in cell division. "If I block it, interaction can't take place and hence cell division does not occur, the tumor stops growing and it will never manifest itself as the aggressive form of cancer called metastasis", she said.

Dr. Pastrana-Ríos, along with students and research assistants Zuleika Sanoguet, Daniel Narváez and Ana María Gómez, have published several scientific articles on efforts to modify the proteins through a process called phosphorylation precisely related to this point. She explained that phosphorylation, is a modification that occurs in specific locations in some protein by others called kinases during a specific moment in the life of the cell. This change has a dramatic impact on the biological properties of the protein. As she pointed out, in the laboratory they analyze the interaction of Centrin protein with a kinase protein called *Aurora A.*

"Today, pharmaceutical companies are making a shift toward biotechnology because diseases are complex and proteins are being used to make drugs", she explained.

University Component

One of the greatest satisfactions of Pastrana-Ríos is to integrate students into research work. She said that in this decade she has managed to train 60 undergraduate students of which 95 per cent have continued into graduate studies, some in medicine, and others are in the biotechnology industry.

Her laboratories host students from different disciplines such as premed, biotechnology, biology, microbiology, chemistry and chemical engineering. "The concept is that we can communicate in only one language because they are different areas of

science. My other goal is to expose them beyond my labs", she expressed, indicating that the students had the opportunity to complete internships outside Puerto Rico in places such as the Mayo Clinic and Vanderbilt University.

On the other hand, she emphasized the importance of young undergraduate students publishing articles. "Publishing in scientific journals is the beginning of a career in the field of science for these students and an incentive beyond academic courses, where they see the application of what they have learned. Class notes get lost, they disappear, you enter the next stage in your training and they're not with you anymore. However, a publication is like a book, still with you, it perpetuates you, and outlasts your life. That is my gift to them, giving them the value they deserve for all their effort", she said.

And how is the UPRM inserted in global efforts to study cancer? questioned **Sin Límites.** "I believe that the UPRM has the potential to contribute to cancer research, in the sense that we have managed to maintain some international collaborations. We have many projects that can bring greater exposure to Puerto Rico and from them we can begin to assess the excellence in science that contributes to health", she specified stressing that they will always require the collaboration of graduate and postdoctoral students.

"We will continue studying proteins in multidisciplinary projects which will succeed in creating an impact in the short and medium term. The reason for success should be to be able to continue exploring the limits; with this come new ideas and with new ideas comes motivation", concluded Pastrana-Ríos.