Maria G. Castro: science is a highly collaborative endeavor that transcends different barriers!

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Editor's note

Brain cancer is one of the deadliest cancers among children and adults under 40. Just in the United States alone, an estimate of approximately 23,000 adults and 3,000 children will be diagnosed with a brain or central nervous system (CNS) tumor in 2018 (1). Brain tumors, which are estimated to claim over 16,000 lives in the current year, reduce life expectancy by an average of 20 years (2). Treatment of brain tumors is challenging as it is associated with our most vital organ. In view of this dire situation, research agencies like National Institutes of Health (NIH) and National Institute of Neurological Disorders & Stroke (NINDS) have been offering hope to improve the management and treatment of brain tumors by providing funding support to researchers who are making painstaking efforts in the field.

Over the years, Prof. Maria G. Castro from the University of Michigan Medical School, Michigan in the US has been studying pediatric and adult brain cancer biology and therapeutics and aiming to develop novel anti-cancer therapies based on immune therapeutics to inhibit tumor growth and recurrence. Her work has been supported by NIH, NINDS, Leah's Happy Heart Foundation, Chad Tough Foundation, The Phase One Foundation and many others. *Translational Cancer Research* (*TCR*) is happy to interview Prof. Castro this time with a focus on understanding the key biological differences between pediatric and adult brain cancers, the mechanisms of immune therapeutics in developing novel brain tumor treatments, the role that tumor immune-microenvironment plays in both tumor progression and therapeutic response, as well as some interesting and challenging aspects of brain tumor research.

Expert introduction

Maria G. Castro, PhD, currently serves as the R.C. Schneider Professor of Neurosurgery, and Professor of Cell and Developmental Biology at the University of Michigan Medical School, Michigan, the US (*Figure 1*). She is also the Director of NIH Cancer Biology Training Grant and a Steering Committee Member of Woman of Color in the Academy Project (WOCAP).

Figure 1 Prof. Maria G. Castro.

Prof. Castro's research focuses on epigenetic regulation of cancer progression, uncovering the role of oncometabolites in the brain tumor microenvironment (TME), and the development of new therapies for adult and pediatric gliomas. Her team is investigating the role of the tumor immune-microenvironment in tumor progression and response to therapeutics, crosstalk between cancer cells and hematopoietic stem/progenitor cells, and mechanisms affecting the migration of immune cells from peripheral lymphoid organs to the TME. The study of these basic immunological mechanisms is expected to lead to clinical implementation and develop novel treatments for brain tumors based on immune therapeutics that targets inhibition of tumor growth and recurrence (*Figure 2*).

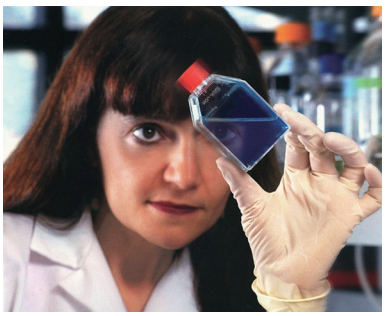

Figure 2 Prof. Castro has been studying pediatric and adult brain cancer biology and therapeutics for years.

Interview

TCR: What are the major differences between pediatric and adult brain cancer biology and therapeutics?

Prof. Castro: Adult and pediatric patients with high-grade gliomas show notable differences in tumor aggressiveness, histology, and tumor progression. Recently, with the advent of next generation sequencing technologies, it has been possible to sequence the genomes of pediatric and adult gliomas. This demonstrated the presence of different and specific genetic lesions/mutations/deletions in both adult and pediatric tumors. Sadly, little funding has been devoted to pediatric brain cancer research, although it is now the leading cause of cancer related deaths in children! This has led to the use of similar treatment modalities in children and adult patients. The consequences have been devastating—adult treatments do not work in children, causing terrible side effects in children that have undergone radiation, and leaving them severely disabled and impaired for the rest of their lives. More funding and research are needed to improve this dire situation and to develop improved treatments for both adult and pediatric patients harboring these deadly and devastating brain cancers.

TCR: What is the significance of studying the molecular profile of glioma?

Prof. Castro: It provides a window into novel therapeutic targets and signaling pathways that may be differentially expressed within the tumor. It also provides information related to the similarities and differences, at the genomic level, between tumors that histologically may seem similar. It furthers our understanding of the biology and behavior of these aggressive tumors.

TCR: How will these studies assist the development of therapeutics in the long run?

Prof. Castro: Uncovering novel mutations, gene deletions, and other genomic alterations, will in turn lead us to novel druggable pathways, mutations, gene fusions, which ultimately might provide more effective therapies for these devastating cancers. In addition, knowing which genetic lesions are present in each type of brain cancer will enable us to develop better models in which to test novel therapeutics, a necessary step before their implementation in the clinic.

TCR: Your research program aims to develop novel treatments for brain tumors based on immune therapeutics. Can you tell us the mechanisms of this novel approach?

Prof. Castro: Our immune-mediated therapeutic approach for high-grade gliomas, both in adults and children, involves using gene therapy as a tool to deliver therapeutic genes into the glioma microenvironment. We use replication deficient, recombinant adenovirus (Ad) vectors as delivery vehicles to deliver two therapeutic genes. The first encodes herpes simplex virus type 1 thymidine kinase, an enzyme that converts the prodrug, Ganciclovir, to a nucleotide analogue that gets incorporated into duplicating DNA in actively dividing cancer cells. This causes cell death, release of tumor antigens and release of molecules that activate antigen-presenting cells within the TME. The second encodes a cytokine called Fms-like tyrosine kinase 3 (Flt3L), which recruits professional antigen presenting cells into the TME. These antigens presenting cells are called dendritic cells (DCs). The activated DCs migrate to the draining lymph nodes, where they present tumor antigens to CD8 T cells. These cells in turn recognize the glioma antigens presented by the DCs, and undergo cell expansion. These activated, glioma specific cytotoxic CD8 T cells travel back to the tumor site, killing any remnant tumor cells within the brain. Our approach also generates anti-glioma immunological memory, which elicits tumor cell death in case of recurrence. Thus, our approach not only eliminates the primary tumor, but also prevents glioma recurrence.

TCR: What has been the effectiveness of this approach so far? What have to be done further to optimize it?

Prof. Castro: Our approach is currently being tested in a Phase I clinical trial for adult patients with high grade

glioma at the University of Michigan, Department of Neurosurgery. We still have 4 more patients to go in order to complete the trial and report the results. Nevertheless, phase 1 trials are designed to assess treatment safety, so the overall efficacy of the treatment will need to await larger, controlled, phase 2 clinical trials. So far, the treatment has proven to be safe and our published data using glioma pre-clinical models has demonstrated that the approach is effective and safe. In order to make the treatment even more powerful, it could be combined with immune checkpoint blockade, i.e., anti-programmed cell death ligand 1 (anti-PD-L1) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies. In addition, our strategy could also be combined with novel chemotherapeutic drugs, as they become available.

TCR: Technically speaking, what role does tumor immune-microenvironment play in tumor progression and response to therapeutics?

Prof. Castro: The tumor immune-microenvironment (TME) plays a critical role in both tumor progression and therapeutic response. We and others have shown that the TME in gliomas is highly immune suppressive and this is partly what enables tumor progression, as the immune system of the host is blocked from recognizing and killing proliferating tumor cells.

In addition, the immune suppressive TME will also block the efficacy of immune-mediated therapies. We have uncovered that gliomas are highly infiltrated with a type of immature immune cell, myeloid derived suppressor cells (MDSCs), which are very powerful inhibitors of cytotoxic anti-glioma T cells. By blocking MDSC activity using a specific blocking antibody it is possible to restore tumor killing by T cells. It is also possible to block immune checkpoints using specific antibodies, therefore restoring normal immune functions in the tumor bearing hosts, and thus enhancing therapeutic efficacy.

TCR: What have been the challenges encountered during research?

Prof. Castro: The most challenging aspect of my work as a scientist is dealing with failure and uncertainty! Most experiments will fail and you never know what and when things will work. This is because we are dealing with the unknown and are aiming to discover how things work: how cancers keep growing, why therapies do not work, etc. Science requires resilience, confidence that we will eventually find the answers, and that we will solve important and meaningful problems. That our work will make a difference. One of the most memorable examples of this is when we received the comments from a grant that we submitted to the NIH. Although the reviewers were overall positive and liked our proposal, our score did not quite make the funding cut. The most damning comment stated: "These researchers have done extensive and elegant work to show the mechanisms by which their gene therapy works at eradicating aggressive brain tumors in rodent models; they now need to test their approach in human patients." Although it felt devastating at the time, this comment is what propelled us to move forward and apply to the Food and Drug Administration (FDA) to seek authorization to test our immune mediated gene therapy approach in the clinic!

TCR: What do you regard as the most interesting aspects of research?

Prof. Castro: The most interesting aspect of research, is pushing the boundaries of what is known, discovering new knowledge that will make a difference, either basic scientific knowledge or advancing medical treatments for patients.

Another aspect that I love is mentoring and interacting with young students and trainees. They bring fresh ideas and insights to my daily work.

I also love interacting with colleagues from all over the world; their collegiality, generosity and altruism inspire me every day! My work is highly multidisciplinary and without the help of selfless colleagues that share their knowledge, knowhow and reagents, progress would be much slower. Science is a highly collaborative endeavor, and scientific interactions transcend religious, racial, socioeconomic and geographical barriers.

TCR: As a professor, what would be your advice to young researchers who would like to pursue their careers in your field?

Prof. Castro: Focus on your own goals and your own path, do not compare yourself to others: we are all different. Enjoy the trip, the ride, the process, do not worry so much about the endpoint, life is what happens to us now! Engage in your work with your whole heart, with passion; care about what you do every day, every minute. Care about and engage with your colleagues, be courteous, be generous, learn to network. Importantly, seek mentors in the various

aspects of your career and your personal life, as they will help you, and will be instrumental for you to achieve your dreams and your goals! Never listen to nay-sayers! Always move forward, one day at a time!

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