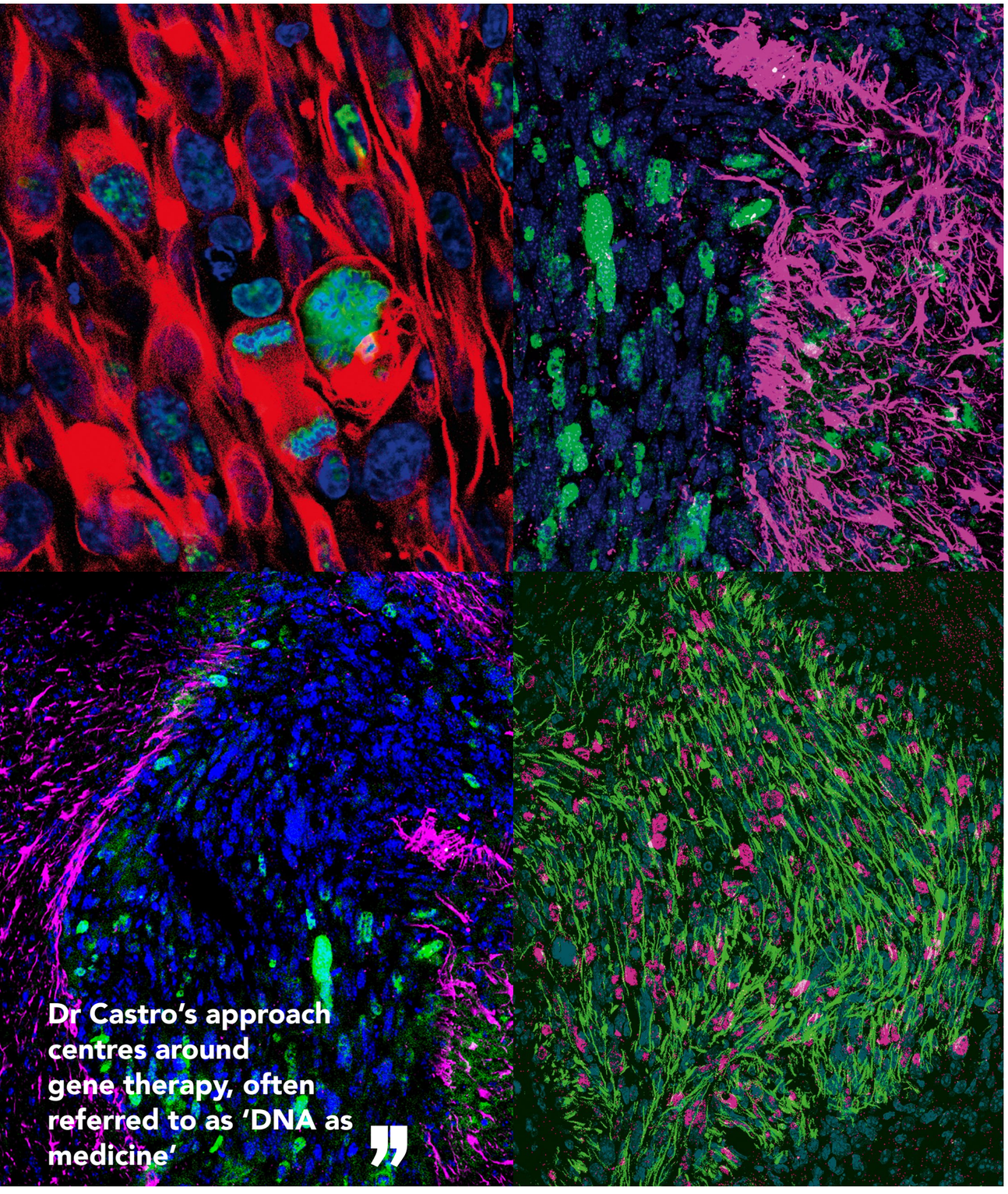


Dr Castro's approach centres around gene therapy, often referred to as 'DNA as medicine'

Recruiting the immune system to help tackle brain cancer

Dr Maria Castro, Professor of Neurosurgery and Cell and Developmental Biology, at the University of Michigan Medical School, is an award-winning cancer biologist, who has dedicated her working life to improving outcomes for people diagnosed with high-grade brain tumours, known as glioblastoma. She has recently embarked on a ground-breaking clinical trial that could offer fresh hope to brain tumour patients.

Glioblastoma is a frightening diagnosis with a bleak prediction. It is a fast-moving and destructive form of brain cancer that affects people of all ages, including children. Prognosis is poor since treatment options are limited and recovery rates low, with an average survival time of 18 months. Brain tumours are the biggest cancer killers of children and adults under 40, and the need for treatments is urgent. Slow progress has been made over the last decades, despite dedicated research by researchers across the world.

CURRENT TREATMENTS

Traditional brain cancer treatments, consisting of surgery to reduce or remove the tumour followed by chemotherapy and radiotherapy, have limited effectiveness and success can be short-lived, with tumours often returning within a year. Diagnosis often happens late as classic symptoms such as seizures often manifest over a number of months or even years before patients are referred for a scan to identify a tumour. People may also experience excruciating headaches and nausea and their friends and family may find that they are acting out of character or displaying unusual behaviours.

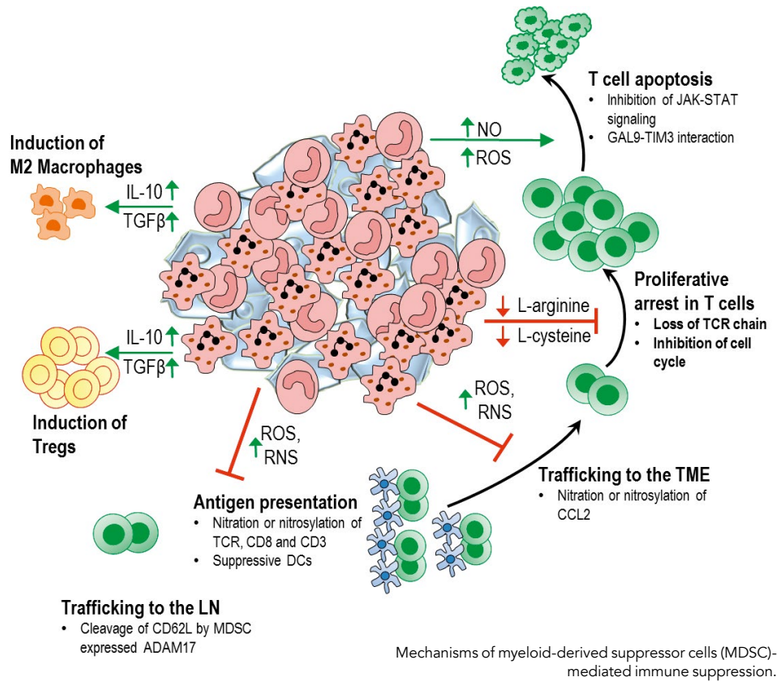
Glioblastoma commonly referred to as Grade 4 stage tumours, are particularly aggressive and likely to spread. A huge challenge of treating glioblastoma is that they can be diffuse, with small pockets of infiltrative cells causing reappearance of tumours, even when the bulk mass has been surgically removed. One pioneering researcher who is aiming to bring hope to patients is Dr Maria Castro. Based at the University of Michigan, Dr Castro is focused on developing treatments for patients with glioblastoma to transform the currently bleak prognosis.

GENE THERAPY

Dr Castro's approach centres around gene therapy, often referred to as 'DNA as medicine'. Gene therapy involves using biological vehicles, known as vectors, to deliver 'good' genes to the patient. Scientists take vectors, based on viruses, and amend them with therapeutic DNA, before directly administering them to the patient. The nature of viruses means that they will infect tumour cells, which means that the therapeutic genes will elicit their beneficial anti-tumour effects around the injected area. A major hurdle to gene therapy is the response of the immune system of the patient, which can suppress the effectiveness of the therapy long-term. To overcome this, Castro's team developed novel approaches to adenoviral vectors, known as high-capacity helper-dependent adenoviral vectors (HC-Ad), which are not detected by the host immune system.

THE GLIOMA MICROENVIRONMENT – IMMUNITY

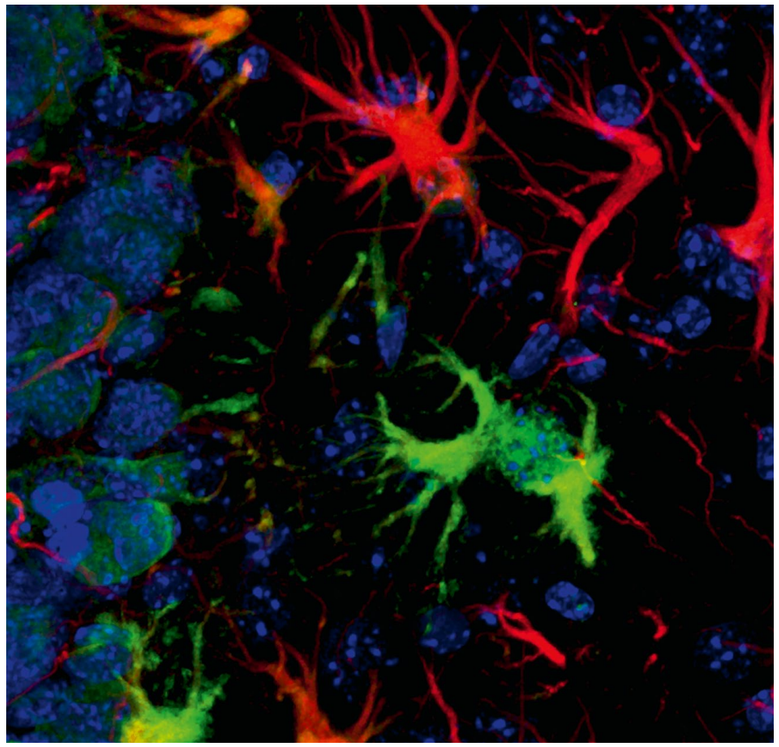
Studying the human brain for research is notoriously difficult due to difficulties in accessing cells or regions which play vital functions. This implies that research into



Mechanisms of myeloid-derived suppressor cells (MDSC)-mediated immune suppression.

new treatments and studying mechanisms of tumour growth in humans is extremely challenging. Innovative mouse models developed by Dr Castro have been one way around this. Key to Castro's work is understanding the growth of tumours in their biological context, referred to as the glioma microenvironment. Her work has shown that by manipulating the immune-suppressing signals in tissue surrounding the tumour, effectiveness of gene therapy can be vastly improved in glioma bearing mice. This is absolutely vital to future clinical implementation, to reduce the likelihood of tumours returning and spreading.

Recently, findings from the Castro laboratory have shown the importance of myeloid-derived suppressor cells (MDSCs) – immune cells that actually supress, rather than enhance, the immune response, thus aiding tumour cells in their damaging growth. MDSCs are associated with poor prognosis, and in recent work, Castro and colleagues showed that blocking these cells in the glioma microenvironment significantly enhanced the effectiveness of gene therapy in mice. Depleting the number of MDSCs reduced brain tumour spread and led to a higher number of mice with glioma who survived in response to the immune-gene therapy. Treated mice exhibited increased length of survival, highlighting how vital the immune system response is to ensure successful treatment.



Fluorescence image showing astrocytes stained in green and microglial cells stained in red. Blue fluorescence indicates cells' nuclei in a tumour bearing mouse model.

FIRST IN HUMAN TRIALS

The two-pronged gene therapy approach has taken an important step forward – approval for testing in a Phase 1 clinical trial in patients. Together with lead investigator Dr Lowenstein and colleagues from the Department of Neurosurgery, Dr Castro is currently running an exciting new clinical trial, offering optimism for people facing brain cancer.

The trial, the first in humans, is an investigation of an approach combining cytotoxic, or cancer killing, gene therapy with therapy to stimulate the immune response. The trial is currently ongoing and open to people aged 18-75 years who have been diagnosed with high-grade glioma.

In this trial, immunotherapy is based on reprograming the microenvironment of the tumour and recruiting immune cells – known as dendritic cells – directly into the tumour mass. After killing cancer cells with a gene therapy vector, the second vector, which encodes *Flt3L* comes into play – encouraging the migration and propagation of dendritic cells. This boosts the patients' anti-cancer immunity and the effectiveness of the cytotoxic agent.

The trial is based on promising pre-clinical findings showing the important effects of dendritic cells in the initiation of the anti-tumour response and anti-tumour 'memory' enacted by the immune system of the patient – a phenomenon referring to immune cells' increased likelihood of responding to previously-encountered pathogens. In pre-clinical trials, this approach led to a decrease in tumour size in mouse models. If successful, this immune memory will be a vital tool against the return of tumours in people who have already been treated.

FUTURE WORK

Dr Castro was named 2016 Javits Neuroscience Investigator Award from the National Institute of Neurological Disorders and Stroke, recognising her commitment to brain cancer research and to developing therapeutic approaches. The award is a reflection of the exciting strides Dr Castro has made in identifying therapeutic targets and has also provided $2.8million in research funding to support her vital work, a financial boost that has allowed for planning of long-term projects investigating cancer therapies.

Results will be available from the gene therapy clinical trial towards the end of 2018. Until then, Dr Castro and her team continue to search for therapies that are safe, effective and acceptable, focusing on innovative approaches that could truly transform patients' lives.

Dr Castro is currently running an exciting new clinical trial, offering optimism for people facing brain cancer"

Q&A

What made you want to study brain cancer?
Malignant brain cancer has a very bleak prognosis both for adult and paediatric patients. In view of the disappointing advances that have been made, in terms of finding a cure or developing treatments that substantially prolong survival, this drove me to devote my scientific career to working towards developing novel therapeutic approaches to improve patients' life expectancy. Also, malignant brain tumours have become the main cause of cancer related deaths in children. In addition, due to the nature of their developing brain, radiotherapy in children elicits very severe short and long term adverse effects, including severe disabilities, thus, developing alternative efficacious treatments is of critical importance. This quest is best pursued in an academic setting, due to the small number of patients affected, with lack of interest from the big pharmaceutical sector. It became even more pressing and meaningful for me to work on alleviating suffering in this young brain tumour patient population.

Do you think you will see a treatment for glioma in the upcoming decades?
Definitively! I think malignant glioma, just like many other terrible diseases, such as AIDS, will become a chronic disease, manageable with new therapeutic options, such as gene therapy or immunotherapy. I think the most powerful therapeutic approach will be achieved by combining the current standard of care with novel strategies that attack the cancer using different mechanisms, such as killing the cancer cells, blocking their invasion, blocking immunosuppression, stimulating an effective anti-tumour immune response.

What are your next steps for your work in immunotherapy for glioma?
My next steps in relation to developing and implementing novel immunotherapy approaches for malignant brain cancers, for both and adult and paediatric patients are to use the recently developed genetically engineered mouse glioma models which harbour all the genetic alterations encountered in the human tumours, within a context of a fully functional immune system to test novel immune-mediated approaches. These would include combination therapies which will use our immune-mediated gene therapy strategy together with strategies that block the immunosuppressive tumour microenvironment, i.e., depletion of MDSCs, use of immune check point blockade.

Do your findings have relevance to other (non-brain) cancers?
Yes, the approach we developed could be applied to metastatic brain cancers, such as breast, melanoma, prostate, lung. All these cancers can metastasize to the brain, where they could be treated with the immune-mediated gene therapy approach we developed. In addition, it could also be implemented for the treatment of other, non-brain located solid cancers. Good candidates for our treatment could be melanoma, breast, lung, ovarian and pancreatic cancer patients.

What are your hopes for the future of brain cancer research?
My hopes for the future of brain cancer research is that more funding should be devoted to studying the biology and the development of novel treatments for these devastating solid cancers. One major challenge is that due to the fact that these tumours are relatively rare, the pharmaceutical companies do not invest in large efforts which are critical for developing novel therapies. This could be bypassed by increased funding from government funding agencies. Also, the international community needs to come together in order to share resources, patient data, and molecular profiles of the tumours analysed. Much more concerted actions from scientists, clinicians, government agencies and the public in general will be needed in order to find a cure for these devastating cancers.

Detail

RESEARCH OBJECTIVES

Dr Maria Castro's research interests include brain cancer biology, development of immune-therapeutics for both paediatric and adult malignant brain cancer.

FUNDING

- National Institutes of Health (NIH)
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COLLABORATORS

- Dr Pedro R. Lowenstein, Dr Karin Muraszko, Dr Sriram Venneti, Dr Daniel Orringer, Dr Jason Heth, University of Michigan Medical School
- Dr Mats Ljungman, Dr Sofia Merajver, Dr James Moon, Dr Anna Schwendeman, Dr Joerg Lahann, University of Michigan
- Dr Maria (Ken) Figueroa, University of Miami Miller School of Medicine
- Dr Shawn Hervey Jumper, University of California San Francisco
- Dr Chris Jones, The Institute of Cancer Research, London, UK

BIO

Maria G. Castro, PhD, is the R.C. Schneider Professor of Neurosurgery, and Professor of Cell and Developmental Biology, at the University of Michigan Medical School. She received her PhD from the School of Medicine at National University of La Plata, Argentina. Dr Castro completed her postdoctoral training at the National Institutes of Health in Bethesda, Maryland.

CONTACT

Maria G. Castro, PhD
R. C. Schneider Collegiate Professor of Neurosurgery, Dept of Neurosurgery,
Dept of Cell & Developmental Biology,
Director of the Cancer Biology Training Grant,
University of Michigan Medical School,
4570C MSRB II
1150 West Medical Center Drive
Ann Arbor, MI 48109-5689, USA

E: mariacas@umich.edu
T: +1 734 764 0850
W: https://medicine.umich.edu/dept/neurosurgery
W: https://medicine.umich.edu/dept/cell-developmental-biology