Towards a universal treatment for viral brain infections

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What is the problem?

Viral infection of the brain (viral encephalitis) is a dangerous condition that mainly affects people with a poor immune system (the system which protects us from infections), such as infants, the elderly and the immunosuppressed.
There are limited treatments for this disease and those available only work against certain viruses. As a result, death rates are high, and few people recover without lasting brain damage.

What are we interested in?

We are interested in developing a "universal" treatment for viral encephalitis that offers protection against a broad range of viruses and can be administered as soon as the disease is suspected. This would prevent the patient's condition worsening whilst trying to determine the causative virus, thereby improving disease outcome and reducing the risk of permanent brain damage. To do this, we are investigating a class of proteins called IgM antibodies as a possible therapeutic agent. IgM antibodies are found in the cerebrospinal fluid (CSF) (a watery liquid found in the brain and spinal cord) of multiple sclerosis (MS) patients. MS patients are often prescribed immunosuppressive drugs and can succumb to viral encephalitis as a result. The presence of these IgM antibodies in MS patient CSF is correlated with reduced risk of developing viral encephalitis.

What did we do?

We tested one of these antibodies (named "O4") in our "brain in a dish" cell culture system. This system contains all the cells of the central nervous system (CNS) (the brain and spinal cord), allowing us to model in the lab what occurs in the human brain. We first investigated whether our antibody could increase the expression of genes involved in the anti-viral immune response. We then explored whether the antibody could protect against a virus which infects the brain, called Bunyamwera virus (BUNV).

What did we find?

Using a technique called RT-qPCR to measure the activity of specific genes, we found that O4 could increase expression of genes involved in the immune system's anti-viral response in our CNS cultures (see Figure 1). We also investigated which types of cells were expressing these protective genes, using a technique called fluorescent in situ hybridisation. We found that all major cell types in our culture system could express these genes (see Figure 2), indicating that O4 could have a protective effect on all cells of the CNS. Cells pre-treated with O4 and infected with BUNV were protected against the virus, with significantly reduced numbers of infected cells being observed in our "brain in a dish" cultures (see Figure 3).

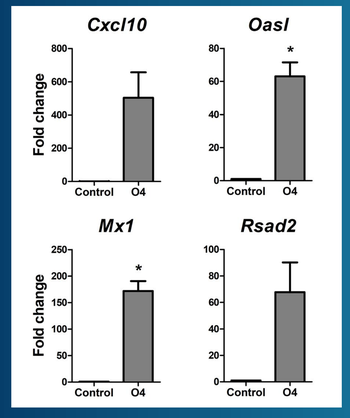

Figure 1: O4 increases expression of anti-viral genes *(Cxcl10, Oasl, Mx1 and Rsad2)* in our "brain in a dish" CNS cultures.

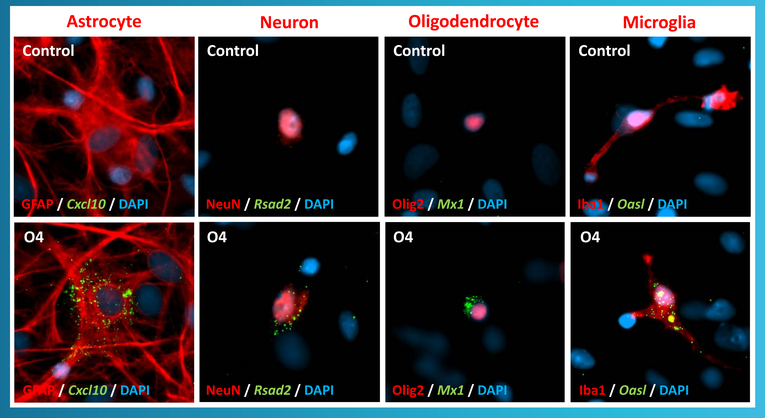

Figure 2: Anti-viral gene expression of *Cxcl10, Rsad2, Mx1 and Oasl* can be observed in major cell types of the CNS. Cell types were identified using different red fluorescent markers (astrocytes = GFAP, neurons = NeuN, oligodendrocytes = Olig2 and microglia = Iba1). Green dots represent anti-viral gene transcript within these cells. Blue DAPI shows cell nuclei.

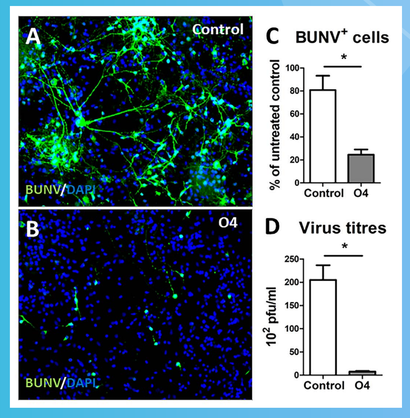

Figure 3: O4 protects against BUNV infection as shown by a decrease in virus-positive cells (green staining in **(B)** compared to **(A)**) and by counting the virus positive cells **(C)** and concentration (titre) of virus particles **(D)**.

What does this mean?

This means that the IgM antibody O4 can increase the expression of a broad anti-viral immune response in the CNS that is sufficient to protect against a virus that infects the brain. This makes O4 a potential candidate for treatment of viral encephalitis.

Who am I?

I am a 3rd year PhD student in the University of Glasgow working in the lab of Dr Julia Edgar. For my undergraduate degree I studied Molecular Medicine in Trinity College Dublin, Ireland where I became interested in diseases of the central nervous system. In the Edgar lab, our research is focused on one such disease, multiple sclerosis. I am particularly interested in how inflammation can affect diseases of the CNS. After my PhD I will either continue to work in academic research or move to the pharmaceutical industry.

Lorna started her PhD project entitled *"From diagnosis to function: the pathophysiological significance of intra-thecal antibody responses to lipids in multiple sclerosis"* in 2017 and while principally based at the University of Glasgow, supervised by Dr Julia Edgar, she is also working closely with EUROIMMUN UK Limited.