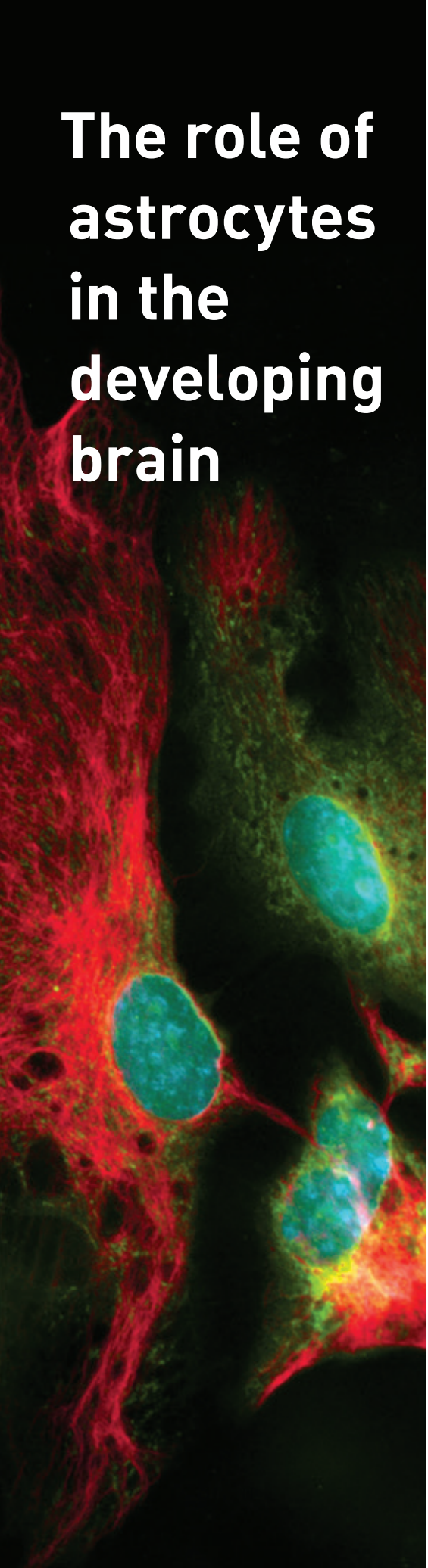
The role of astrocytes in the developing brain



Working together to uncover the involvement of astrocytes in neurodevelopmental processes, **Professor Laurie Doering** and **Dr Angela Scott** discuss what led to their current research practices and the therapeutic interventions they hope to facilitate

Firstly, what is the relationship between Fragile X syndrome (FXS) and autism spectrum disorder (ASD)?

FXS is caused by a defect in the *FMR1* gene located on the X chromosome. FXS is the most common cause of inherited intellectual disability and is one of the principal genetic causes of ASD. Autism and ASD are both general terms for a group of developmental brain disorders with associated behaviours. These disorders are characterised – in varying degrees from person to person – by difficulties in social interaction, verbal and nonverbal communication and repetitive activities.

Can you describe how you became involved with research into FXS and explain what motivates you both?

With different lines of ongoing stem cell research in the lab, we began to explore stem cell therapy in a mouse model of FXS. We asked the question: can we replace the missing gene product seen in FXS using transplants of stem cells? This research paralleled a key 'motivating' discovery in our lab – that normal astrocytes, which are predominant support cells in the brain, express high levels of the FXS missing gene product, especially during early development. This finding opened an area of new research that we continue to study, asking questions about how astrocytes are affected in FXS and whether they affect the development of the brain and offset – or even potentially correct – the altered development in FXS and ASD.

Could you highlight the impact that ASD has on individuals worldwide?

There is no 'cure' for ASD and studies point to an upward trend in its prevalence. It is four to five times more common in boys than girls. Although the spectrum and degree of the disorder varies, individuals with ASD experience a lifelong neurodevelopmental disorder that affects how they interact and relate to others.

What potential do your techniques to correct communication patterns in the brain have for translation into therapeutic strategies in the future?

This is an incredibly exciting time for research in the field of ASD. With technological advances in molecular and genetic epidemiology, researchers now have further insights into the breadth of potential underlying causes of various ASDs. The identification of the possible molecular or genetic underpinnings of ASD will be essential for therapy development, but also poses one of the greatest challenges in the field. New techniques in molecular profiling – which offers important insight into genetic characteristics and unique biomarkers of ASD – provide promising approaches to this problem.

Together with the continued investigation into the cellular basis of the aberrant signals, these techniques will help mould a highly targeted therapeutic approach for ASD. For instance, the discovery of the single genetic mutation underlying FXS has allowed for the creation of genetically relevant animal models of the disorder. Our work has successfully used these models to study subsequent cellular and molecular alterations associated with FXS, and we are highly encouraged about the therapeutic potential of several pharmacological targets we are currently testing.

Do you expect your research on astrocytes to have relevance for other neurological conditions?

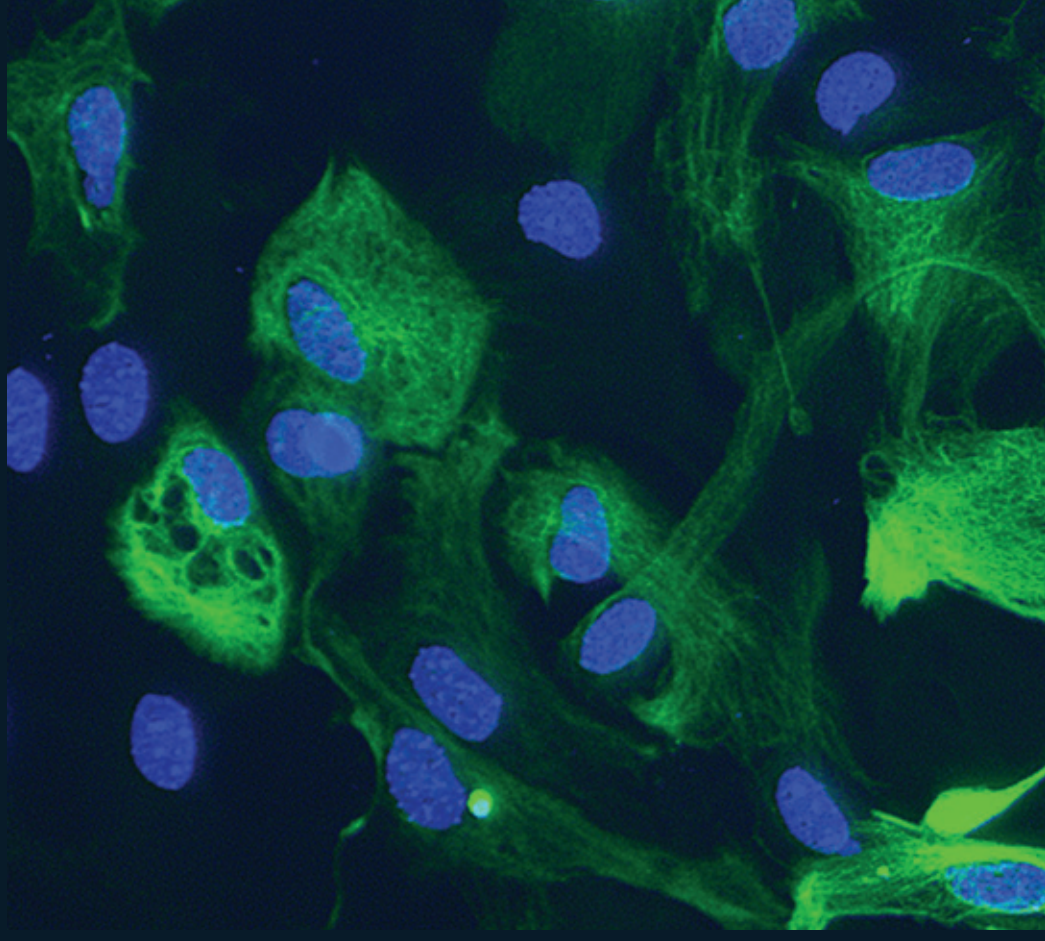
Results from our research indicate that astrocytes can promote corrective developmental changes in neurons affected by FXS. Given this, and the fact that astrocytes are integral to normal brain development, we certainly believe that this research has significant relevance for other disorders, such as epilepsy or schizophrenia. In particular, our work is highly applicable to children diagnosed with developmental delays and specific genetic conditions, such as Rett syndrome.

How do you foresee your research developing in the next few years?

We hope to determine if specific astrocyte factors implicated in FXS are secreted at normal levels during the critical phases of brain development. We are currently examining key molecular pathways involved in astrocyte-neuronal communication and investigating whether possible alterations in molecular and physiological signalling is associated with the disorder. Eventually, we will be able to link the key astrocyte factors with the molecular steps in the altered brain development that leads to the neurodevelopmental conditions of FXS and ASD. We hope that this research will heighten awareness of the importance of the astrocyte during brain development, and, in turn, initiate new streams of research in other laboratories.

Autism and Fragile X syndrome

Collaborative basic research at **McMaster University** in Canada aims to understand the developmental changes in the brain that lead to the social and intellectual problems associated with Fragile X syndrome, autism and other neurodevelopmental conditions. Studies on the role of astrocytes have already led to fascinating discoveries



FRAGILE X SYNDROME (FXS) is a genetic condition that leads to a range of developmental problems, including learning disabilities and cognitive impairment. Interestingly, it is twice as common in boys than girls, with approximately one in 4,000 males and one in 8,000 females affected. The condition is also one of the leading causes of inherited intellectual disability, and one of the most significant genetic causes of autism spectrum disorders (ASD). Indeed, almost half of all children with FXS meet the criteria for a diagnosis of autism, which is itself a developmental brain disorder with associated behaviours.

Children with ASD typically display symptoms before the age of three and, while the spectrum is extremely broad, typical manifestations of the condition affect social interaction, communication, interests and behaviour. While speech, language and occupational therapies are available in addition to educational support, there is currently no 'cure' for ASD.

As research and clinical work over the past few decades have led to a broadening of what is conceptualised as autistic disorders, so too has the recorded incidence. As the prevalence continues to rise dramatically, the financial costs associated with care and education are having a significant economic impact. Thus, the need for new interventional strategies becomes an increasingly pressing requirement, not just for ASD, but for FXS and other related disorders.

CORRECTING NEURONAL FUNCTION

In an effort to improve our understanding and work towards the development of better therapies for neurodevelopmental disorders, a team based at McMaster University is conducting research to identify the molecular alterations in the brain responsible for autistic features. Led by Professor Laurie Doering, the team is studying the cell biology of astrocyte-neuron communication as a means to correct neuronal function in autism. It has been shown that many neurodevelopmental disorders can be characterised by abnormal communication, so the researchers have concentrated on studying the function of astrocytes.

Astrocytes are brain cells that manufacture the substances that enable and secure proper communication between other brain cells. In the developing brain, astrocytes are extremely important for the organ's proper growth and function and, as an alteration of communication between brain cells can lead to many of the defects associated with autism, astrocytes have been identified as an interesting topic of focus. "In a relatively recent discovery, it was found that neurons rely on astrocytes to regulate the formation and function of their synapses," explains Doering. "This has emphasised the potential role of astrocytes in ASD and, particularly, FXS."

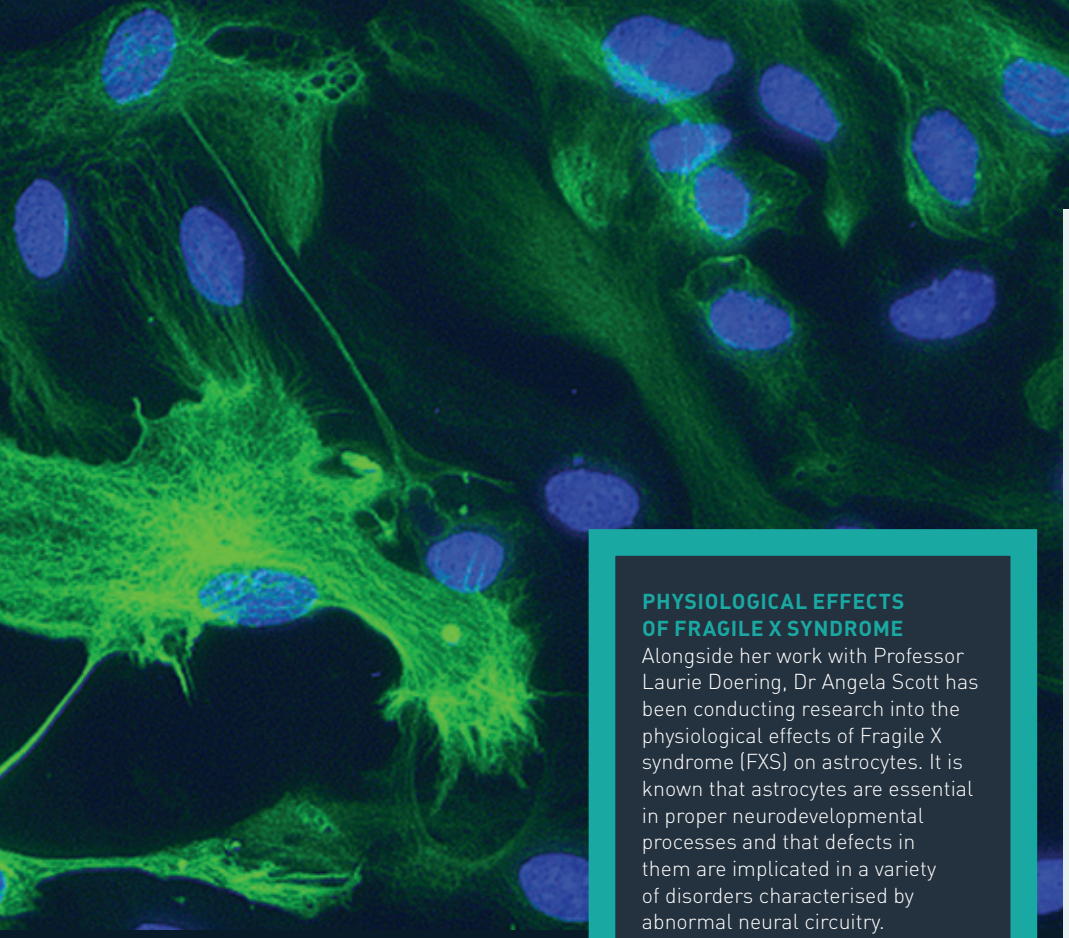
ABERRANT ASTROCYTES

The team has therefore comprehensively studied astrocyte-secreted factors in the hope of preventing abnormal neuronal circuitry at the molecular, cellular and physiological levels. Importantly, the researchers have managed to identify a link between astrocyte function and ASD. "We, among others, have found that aberrant astrocyte signalling alone can indeed produce hallmark FXS-associated synaptic defects to otherwise healthy neurons," explains Doering. "Importantly, the replacement of these signals by naive astrocytes can reverse the observed defects, which highlights the integral nature of astrocyte-neuron communication to the predisposition of these neurodevelopmental disorders."

ASTROCYTES IN TISSUE CULTURE

Professor Laurie Doering's laboratory has produced a time-lapse video that shows the cell movement of astrocytes combined with the expansion and retraction of the plasma membranes.

To view the video, visit: **https://vimeo.com/131666732**



PHYSIOLOGICAL EFFECTS OF FRAGILE X SYNDROME

Alongside her work with Professor Laurie Doering, Dr Angela Scott has been conducting research into the physiological effects of Fragile X syndrome (FXS) on astrocytes. It is known that astrocytes are essential in proper neurodevelopmental processes and that defects in them are implicated in a variety of disorders characterised by abnormal neural circuitry.

Adenosine triphosphate (ATP) plays an integral part in the regulation of synaptic development and function, so Scott and her colleagues are comparing the physiological responses of astrocytes isolated from both normal mice and transgenic mice used to model FXS. Differences detected in the sensitivity of FXS astrocytes to ATP and similar signals, will provide insight into the underlying atypical molecular communication during development in FXS.

Ultimately, an increased understanding of the signalling involved in FXS – and other brain disorders associated with impaired development – could identify targets for new therapeutics.

Having identified the source of the defects associated with neurodevelopmental disorders, the team is now intent on using different biological and genetic techniques to correct the communication patterns in the brain. As these defects are likely to be associated with signalling pathways regulated by the protein FMRP, the team utilises FXS animal models to highlight possible intervention strategies. Indeed, by identifying and applying substances from normal astrocytes to FXS brain cells, Doering and his team hope to offset the development of abnormal communication in the brain.

DETAILING NEURODEVELOPMENTAL DISORDERS

Ultimately, this important research will help determine the precise methods of counteracting many of the intellectual and social disabilities associated with autism. So far, technological advances have enabled detailed insights into the possible underlying causes of various neurodevelopmental disorders, thereby ushering in a new era for research in the field of ASD and other related conditions.

Moving forward, existing findings and future research will foster the development of new interventional treatment strategies for social disability disorders, making a difference to the lives of millions of people around the world.

ASTROCYTES AND THE TREATMENT OF AUTISM SPECTRUM DISORDERS

OBJECTIVE

To study the cell biology of astrocytes in normal development and in neurodevelopmental disorders with a focus on autism and Fragile X syndrome.

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DR LAURIE DOERING has a PhD in developmental neuroscience, with postdoctoral training at McGill University and the Montreal Neurological Institute. He is Professor of Pathology and Molecular Medicine at McMaster University's Michael G DeGroote School of Medicine. His expertise is in stem cell biology, tissue culture, molecular imaging and animal models of nervous system dysfunction.

DR ANGELA SCOTT completed her PhD in neurophysiology at the University of British Columbia and worked as a postdoctoral fellow at the University of Edinburgh and McMaster University. The recipient of numerous research awards, Scott has an interest in the cellular mechanisms that govern development and recovery in the nervous system.