Which experiences from your academic and professional background do you think have played the biggest role in shaping your research today?

I am a qualified doctor and spent a year working as a doctor, but then turned to science. I was lucky to experience first-hand the pioneering research into the function of the neuromuscular junction by Nobel laureates Bernhard Katz and Bert Sakmann, and Ricardo Miledi at University College London in the late 1960s, which was crucial for the understanding of transmission across synapses in the peripheral and, later, the central nervous system. In 1969, Miledi had already used snake toxins to purify the postsynaptic ‘acetylcholine receptors’ that received the acetylcholine signal from the nerve, and after three very unproductive years in a different department, I began to work with Miledi on these receptors and the neurological disease myasthenia gravis, beginning a collaboration with neurologist John Newsom-Davis. All of my work today stems from these very fortuitous experiences.

Can you discuss some of the work taking place at the Vincent lab? Why are you focusing on antibodies in particular?

If a patient has an antibody to a neuromuscular junction or central nervous system receptor, or another membrane protein, it is highly likely that their symptoms will improve if you can reduce the levels of the offending antibodies. Therefore, if a patient presents to a neurologist with symptoms of muscle weakness, or epilepsy, for instance, it is now common to ask whether they have one of the known antibodies. It is akin to performing a genetic test to identify a particular form of disease. My laboratory has two main aims. First, to help diagnose these patients, which we do by running a clinical service that is used by most hospitals in the UK, and many around the world. And second, to identify new antibodies, look for them in patients with diseases for which there is no current diagnostic test, and study how the antibodies affect neurological functions. We are also interested in asking whether there were antibodies to neuronal proteins in some pregnant mothers whose children subsequently developed diseases such as autism or schizophrenia.

Are you collaborating with any individuals, groups or institutions that you would like to highlight?

We collaborate worldwide with neurologists on many clinical studies of individual patients and examine the antibodies and clinical features of patients with specific neurological diseases. At the moment, we have a particular interest in improving the diagnosis and treatment possibilities of patients with myasthenia gravis, which involves many of the myasthenia centres in the UK, Europe and Japan. We are also looking for specific antibodies in children and adults with unexplained epilepsy or psychosis, partly in collaborations with the Institute of Psychiatry in London, and the Universities of Sydney and Groningen. The maternal antibody studies are being performed in collaboration with the Department of Economics and Business – National Centre for Register-based Research in Aarhus Denmark.

What are your main objectives over the next five years?

I am already past the normal retirement age but would like to complete some of the projects that have been intriguing me over the last decade or two: looking at the relative roles of serum antibodies and cerebrospinal antibodies in causing central nervous system diseases; showing whether or not maternal antibodies can be an important factor in causing neurodevelopmental disorders in the offspring, using a combination of serum studies and animal models; and exploring whether there is a role for antibodies in patients with some unexplained conditions such as pain or sleep disorders. The main objective must be to leave the Neuroimmunology Group in good hands and with a sensible strategy for the future.

Professor Angela Vincent FRS has had a long and fruitful career in neuroimmunology and has been involved with developing better diagnostics of diseases with an autoimmune basis. Here, she discusses the current priorities of her lab.
Antibody, brain proteins

Starting at the Royal Free Hospital School of Medicine in 1977, and moving to the University of Oxford, UK, in 1988, the Vincent Neuroimmunology Group was created to understand the mechanisms underlying nerve and muscle diseases. The contributions to understanding the links between autoantibodies and neurological diseases has been considerable.

UP UNTIL THE 1960s the brain and other components of the nervous system were a largely mysterious and uncharted territory of the human body, and neurological diseases were diagnosed based on descriptions of symptoms and simple investigations. However, during the last few decades the understanding of neurological diseases has developed beyond recognition and now almost all disorders are investigated in terms of their molecular mechanisms. This paradigm shift was in part due to the increasingly interdisciplinary nature of research, encompassing clinical genetics, physiology, pharmacology and molecular biology. "This now allows any individual disease to be defined at the level of the gene, the protein, the cellular function, the influence on function of the nerve cells, and ultimately, on the behaviour of mouse and man," explains Professor Angela Vincent, who embraced the change in neurology early on in her long career, and is now based at the Nuffield Department of Clinical Neurosciences at the University of Oxford.

Vincent runs the Clinical Neuroimmunology service, analysing patient samples for diagnosis, and has been well placed to carry out work at the interface between the clinical and experimental sides of science. She originally trained as a doctor but joined the eminent neurologist John Newsom-Davis, developing together an interest in myasthenia gravis, a disease that leads to muscle weakness. Newsom-Davis and Vincent then began to make strides in the recognition of other neurological disorders caused by autoimmunity, and set up the Neuroimmunology Group at the Royal Free Hospital School of Medicine.

AN AUTOIMMUNE BASIS FOR A NEUROLOGICAL DISEASE
Autoimmunity plays a well-known role in diseases such as diabetes, but less is known about its role in neurological disorders. In autoantibody diseases, the body produces antibodies that target its own proteins resulting in loss of these proteins or damage to the cells in which they function. The first neurological disease with autoantibodies was myasthenia gravis, a rare disorder of the neuromuscular junction where communication between the nervous system and muscular system is impaired, resulting in muscle weakness. At the neuromuscular junction, the acetylcholine receptor (AChR) is clustered on the muscle surface during development, so that the muscle fibre can efficiently receive the chemical signal (acetylcholine) that is released from the motor nerve; this signal triggers muscle contraction. The AChR clustering is dependent on another nerve signal that activates a protein, muscle specific kinase (MuSK).

For myasthenia gravis, Vincent and Newsom-Davis confirmed that the majority of patients with the disease have antibodies to AChR, resulting in loss of AChR from the muscle fibre surface and consequently the symptoms observed in the disease. Importantly, they showed that removing the antibodies with a treatment called plasma exchange resulted in dramatic clinical improvement. Subsequent work by Vincent showed that some myasthenia patients without AChR antibodies had antibodies to MuSK, resulting in reduced levels and dispersion of AChR due to inhibition of MuSK clustering activity. Understanding which autoantibodies a patient with myasthenia gravis is producing, and how they result in disease, can be key in ensuring they receive the most effective and relevant treatment.

AUTOANTIBODIES AGAINST NEURONAL CELL SURFACE TARGETS
Since 2001, a number of antibodies to brain proteins have been discovered by Vincent and others. These include autoantibodies against parts of the voltage-gated potassium channel complex (VGKC) and the N-methyl-D-aspartate receptor (NMDAR), both linked to brain inflammation (encephalitis) and epileptic seizures.

To measure the antibodies, Vincent uses human embryonic kidney (HEK) cells expressing the expected target of the antibodies. Adding the serum or cerebrospinal fluid (CSF) of a patient with appropriate symptoms, and identifying whether antibodies bind the target expressed by the HEK cells, will determine if the patient has the specific autoantibodies in their serum or CSF. In some cases, it is also helpful to confirm that the antibodies bind to the surface of live brain neurons that can be cultured in the laboratory (see figure above).

The reason for these elaborate and time-consuming tests is that autoantibodies directed towards the cell-surface are more likely to be causative than those that bind intracellular antigens. This is borne out by the treatment responses of many patients,
ANTIBODIES CAN DAMAGE THE BRAIN

OBJECTIVES

To identify antibodies to specific proteins that are essential for brain, nerve or muscle function. Patients with these antibodies have neurological diseases that may include epilepsy, loss of memory, psychosis or abnormal movements, and can be treated by reducing the levels of the antibodies with drugs or other treatments. Babies of mothers who have these antibodies, even if the mothers are not showing signs of disease, may be at risk of neurodevelopmental disorders.

KEY COLLABORATORS

Dr Ming Lim, Evelina Children’s Hospital, St Thomas’ Hospital, London, UK; Professor Oebete F Brouwer, University of Groningen, University Medical Center Groningen, Netherlands; Professor Preben Bo Martensen, Department of Economics and Business - National Centre for Register-based Research, Aarhus, Netherlands; Professor Christian Bien, Mara Hospital, Bethel Epilepsy Centre, Bielefeld, Germany

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ANGELA VINCENT qualified as a doctor, but after practising for one year she obtained an MSc in Biochemistry at University College London. She worked with Ricardo Miledi on acetylcholine receptors in myasthenia gravis, and began a long partnership with neurologist John Newsom-Davis, moving with him and their team to the [Weatherall] Institute of Molecular Medicine in Oxford in 1988. In 1992, she established a national and international referral centre for the diagnosis of immune-mediated neurological diseases, and since Newsom-Davis’ retirement in 1998, she has led the Neuroimmunology Group, researching antibody-mediated neurological diseases. She was elected FMedSci in 2003 and Fellow of the Royal Society in 2011.

both children and adults, who have been identified by the Vincent lab in the last 10 years. The antibodies in these patients now include not only NMDARs and VGKC-complex proteins, LGI1 and CASPR2, but also glycine and γ-aminobutyric acid (GABA) receptors, and surface proteins on glial cells associated with demyelinating diseases. However, how any of these antibodies, which are produced initially in the periphery, gain entry into the brain tissue to cause disease is still hotly debated.

AUTOANTIBODIES AGAINST INTRACELLULAR BRAIN TARGETS

Antibodies to glutamic acid decarboxylase, an intracellular enzyme, are more of a mystery. They are found in a chronic progressive disease called stiff person syndrome (SPS), which leads to extreme muscular rigidity. Work by the Vincent Group showed that these patients often had additional antibodies to neuronal surface proteins that are more likely the cause. In fact, some patients with similar, but more extensive and life-threatening symptoms, have antibodies to surface glycine receptors. These are responsible for controlling many neuronal cell functions, and current experiments in mice are showing that these antibodies can access the brain and bind to the glycine receptors in the brain and spinal cord.

DIAGNOSIS OF TREATABLE AUTOIMMUNE DISORDERS

Partially due to Vincent’s background as a clinician, her work is well translated into informing the diagnoses used for these rare and often severe neurological disorders. If an adult or child presents with symptoms of brain disease and a test of their serum reveals autoantibodies against any of these proteins, the patient’s doctor can make a diagnosis and consider treating with immunotherapies aimed at reducing the levels of the autoantibodies. As Vincent notes, her work on developing and refining patient diagnostics may also develop further: “Together with the tools provided by molecular biology and biochemistry one can also begin to explore why some patients get these diseases, the molecular mechanisms, drug targets and how these differ between individuals, leading to patient-specific approaches to treatments”.

Current work by Vincent’s Group at Oxford includes research on maternal antibodies and their role in causing neurodevelopmental disorders in the future child. This is conducted via experimental techniques, most likely first used by Vincent and colleagues, including a maternal-to-fetal transfer model with postnatal behavioural testing in mice, which can be used to demonstrate the pathological effects of maternal antibodies on foetal development. Through this model Vincent has shown that maternal antibodies that inhibit foetal AChR can be transferred to the foetus, causing musculoskeletal problems in the child. The maternal-to-fetal transfer model is now being used to explore maternal antibodies in autism and schizophrenia. “We have established approaches that we use in our work which are now recognised and used much more widely,” summarises Vincent on the impact of their methodologies.

SOLID GROUND FOR NEUROIMMUNOLOGY

Despite retiring officially in 2008, Vincent continues to run the clinical service, searches for new antibodies and investigates their mechanisms, and lectures widely. The information that Vincent and her team produce can help doctors confirm the diagnosis and likely response to immunotherapies. Vincent’s lifetime achievements were recognised in 2009 with the prestigious Association of British Neurologists Medal, but as she continues to work indirectly and directly for patients with these rare and severe neurological disorders her scientific legacy will be felt for years to come.