Don’t get overexcited! 
Restoring inhibition in neurological disorders

Dr Davies and Professor Moss from Tufts University have collaborated to successfully uncover a new way of treating one of the underlying causes of neurological disorders such as epilepsy and Fragile X Syndrome. Restoring the lost inhibitory action of GABA receptors, their work combats the overexcitation of neurones associated with these conditions.

What first drew you to the investigation of neuronal disorders such as Fragile X Syndrome?
I have had a long standing interest in how neurosteroids modulate GABAARs, especially extrasynaptic GABAARs. When I started my collaboration with Steve, he was already examining how neurosteroids change the phosphorylated state of extrasynaptic GABAARs and we saw a rapid change in the surface expression of functional channels leading to a rise in tonic inhibition. At the same time, there were reports on a reduced tonic inhibition in neuronal developmental disorders such as Fragile X and we thought that boosting the expression of GABAARs would be a novel therapeutic approach. Traditionally, the aim would be to allosterically enhance the channels that are already there in the membrane but we are seeking to increase the number of receptors back to normal levels.

How has collaboration helped in moving the research forward?
We have distinct and overlapping skills: Steve is known for his pioneering work on GABAAR phosphorylation and trafficking. I have experience on recording the currents that flow through GABAAR ion channels and examining subunit-dependent changes in function and pharmacology. Together, we have the experience to examine the broader picture of how changes to protein phosphorylation affect neuronal excitability and how brain circuits are altered.

How did SAGE Therapeutics become involved in the work?
SAGE had an interest in how their neuro-active steroids were modulating synaptic and extrasynaptic GABAARs. When we identified a novel mechanism of neurosteroids changing the phosphorylated state of extrasynaptic GABAARs to increase the trafficking of the receptor, we, together with SAGE, became interested in knowing whether synthetic neuro-active steroids could also work through this mechanism or if it was just naturally occurring neurosteroids that could phosphorylate GABAARs. Discovering that certain synthetic compounds can enhance tonic inhibition through a trafficking mechanism differentiates those SAGE compounds from the typical allosteric modulator often used clinically to control excitation.

What is the next step in realising NAS as a therapeutic agent?
Firstly, we are awaiting results from clinical trials of some neuroactive steroids that are currently underway. However, we still do not understand the mechanistic pathway of how neuroactive steroids alter the phosphorylated state of extrasynaptic GABAAR. Once we know more about the pathway then we could identify more selective compounds. In order for that to happen we are examining different pathways and different interacting proteins. Once the pathway(s) have been identified we could generate novel animal models which will demonstrate the specificity of the compounds generated before going forward into clinical trials.
The human brain is a complex organ and scientists have spent long careers attempting to elucidate the mechanisms underlying its activity. Central to this is the regulation of synaptic activity. A synapse is the point of communication between brain cells, usually neurones, as well as their connection to other tissues such as muscle. Each of these synapses is binding with receptors, proteins inserted into the cell membrane to sense the extracellular signalling molecules which are the messengers of the body. Gamma-aminobutyric acid (GABA) is the neurotransmitter which is exciting the neurones, its role is to inhibit the effect of other transmitters which are stimulating, is still a matter of intense research.

The GABA<sub>A</sub> receptor is a target for therapeutic drugs due to its ability to inhibit excitatory signals from other cells. An increased incidence of epilepsy is frequently implicated in FXS, along with a reduction in expression of a protein associated with the disorder, known as fragile X mental retardation protein (FMR1). A reduction in neuronal inhibition results in complex intellectual and behavioural issues in those with the genetic condition. An increased incidence of epilepsy is also a factor affecting individuals with the condition, and thought to be directly related to the deficits in neuronal inhibition. Using a mouse model of Fragile X in which the FMR1 protein has been ‘knocked out’ through genetic modification, the researchers have shown that it is indeed the mis-trafficking of the GABA<sub>A</sub> receptor in Fragile X Syndrome (FXS). FXS is an autism spectrum disorder, and is the most common form of inherited intellectual disability. Deficits in neuronal inhibition by GABA<sub>A</sub> receptors are frequently implicated in FXS, along with a reduction in expression of a protein associated with the disorder, known as fragile X mental retardation protein (FMR1). A reduction in neuronal inhibition results in complex intellectual and behavioural issues in those with the genetic condition. An increased incidence of epilepsy is also a factor affecting individuals with the condition, and thought to be directly related to the deficits in neuronal inhibition.