Aim

The aim of this project is to determine whether the noble gases Helium, Neon, Argon & Krypton are neuroprotective in *in vitro* models of stroke and traumatic brain injury and to understand their mechanism of action.

Background

Traumatic brain injury (TBI) and stroke are major causes of morbidity and mortality throughout the world, but there are no clinically effective treatments to prevent brain cell death following injury. Experiments in our laboratory first showed that the noble gas xenon inhibits the NMDA-receptor. Our identification of xenon as an NMDA-receptor antagonist led to the idea that xenon might be used as a neuroprotectant. Xenon has now been shown to be neuroprotective in models of ischemia, stroke and traumatic brain injury [3-6] and xenon is beginning clinical trials at the Hammersmith Hospital as a potential treatment to prevent brain damage in babies suffering neonatal asphyxia. Helium, argon, krypton and xenon are all members of the same chemical group of noble gases. The aim of this project is to test the hypothesis that these other members of the series of noble gases (helium, argon and krypton) are neuroprotective using *in vitro* models of stroke and traumatic brain injury, and to determine their mechanism of action.

Experimental Design & Methods

In my lab we have established *in vitro* models of stroke and traumatic brain injury using organotypic hippocampal brain-slices from mice. The organotypic culture protocol is up and running in our lab and we have already used this system to identify the mechanism by which the noble gas xenon protects against ischemic injury (such as stroke). We have shown that xenon inhibits NMDA-receptors by competing for glycine at the glycine-site on the NR1 subunit and that the same mechanism underlies xenon neuroprotection (see Figure 1).

In the stroke model the brain slices are exposed to experimental hypoxia/ischemia by being placed in a chamber without oxygen for a period of 30 minutes. Damage to the slices is quantified by measuring the amount of a fluorescent dye that enters dead cells.

In the model of traumatic brain injury the slices are damaged by dropping a small stylus onto the slice. The resulting injury develops over the 72 hours after injury in a manner that models what happens after brain trauma in humans.

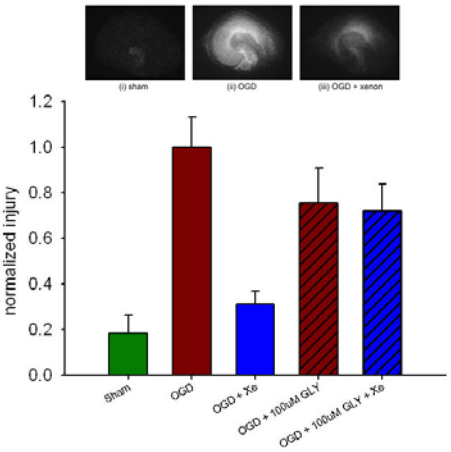

Figure 1 Xenon neuroprotection against hypoxia/ischemia is abolished at high glycine concentration. The bars show injury (PI fluorescence) in organotypic slices 24hrs after oxygen-glucose deprivation (OGD). Xenon (blue) reduces injury by 70%. Adding 100uM glycine does not significantly alter the effect of OGD, (brown hashed) but xenon neuroprotection is abolished (blue hashed). Data are normalised to OGD without xenon or glycine. Sham slices (green) undergo identical treatment but are not exposed to OGD. Data are from an average of 54 slices for each condition. Inset shows typical images of sham, OGD and xenon-treated slices.

Why is this project of interesting?

Xenon is appears to be remarkably effective as a neuroprotectant, however at present xenon is expensive. Helium argon and krypton are much less expensive than xenon. If other inert gases were also neuroprotective, this could represent a major advance in treatment.

The project will involve the following techniques:

Organotypic brain-slice cell culture, fluorescence microscopy, image analysis.

Mr Sukha Sandher, January 2014