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| **Institution:** Imperial College London | | |
| **Unit of Assessment:** 5 – Biological Sciences | | |
| **Title of case study:** A5-4 Discovery and translation of the inert gas xenon as a neuroprotectant | | |
| **Period when the underpinning research was undertaken:** 2000-2006 | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):** Professor Nick Franks | **Role(s) (e.g. job title):** Professor of Biophysics and Anaesthetics | **Period(s) employed by submitting HEI:** 1977 - Present |
| **Period when the claimed impact occurred:** 2014-present | | |
| **Is this case study continued from a case study submitted in 2014?** N | | |

**1. Summary of the impact** (indicative maximum 100 words)

Research at Imperial College showed that the "inert" gas xenon binds to, and inhibits, a particular subtype of glutamate receptors. The over activation of this receptor is known to be pivotal in the brain damage caused following stroke, cardiac arrest or traumatic injury, which suggested xenon might be neuroprotective. The demonstration at Imperial College that this was indeed the case, led to the formation of a company, Neuroprotexeon, with ~35 people working in the UK, USA and Germany, and to the initiation of a pivotal Phase III trial investigating the efficacy of xenon in treating brain injury following cardiac arrest.

**2. Underpinning research** (indicative maximum 500 words)

There is an urgent need for a safe and effective treatment for brain injury following stroke, cardiac arrest or traumatic injury. Current treatments are generally ineffective. The possibility that the noble gas xenon might be used as a neuroprotectant arose from work carried out at Imperial College on the molecular mechanisms underlying general anaesthesia. One of the great attractions in the possibility that xenon might be neuroprotective was that xenon is known to be non-toxic and cannot be metabolised. Therefore, the most frequent reason for the failure of therapeutic interventions - toxicity of the drug or its metabolites - would likely be avoided. Xenon was known to have anaesthetic properties since the 1950s, but its molecular targets were unknown. In 2000 Franks and colleagues followed up an earlier brief report in *Nature* showing that the NMDA subtype of glutamate receptors was the likely target for xenon, with the gas selectively inhibiting its activity at anaesthetic concentrations **[1]**. Because the activation of this ion channel-receptor had already been established as playing a pivotal role in neuronal cell death following injury, this suggested that xenon might act as a neuroprotectant by limiting NMDA-receptor activation; initial patents were filed **[2, 3]**.

Subsequently, in 2002/3, Professors Franks, Maze and their colleagues at Imperial College demonstrated that xenon was, indeed, neuroprotective both *in vitro* and *in vivo* **[4, 5]** and published a further 53 papers **[e.g. 6, 7]** describing neuroprotective properties of xenon and other noble gases. Since these initial publications, there has developed a burgeoning field investigating the neuronal and cardio protective properties of xenon and other “inert” gases, and many hundreds of publications have appeared since the initial report in 2002.

A phase I trial **[8]** assessing gross safety and feasibility of delivering xenon to patients was carried out at Imperial. The basic science showing that xenon was efficacious in animal models of brain injury, together with this trial showing that xenon could be safely delivered to patients, provided the impetus for commercialisation of the technology and funding of a pivotal trial.

**3. References to the research** (indicative maximum of six references)

**[1]** de Sousa SL, Dickinson R, Lieb WR, Franks NP. Contrasting synaptic actions of the inhalational general anesthetics isoflurane and xenon. *Anesthesiology* **92**:1055-66 DOI: 10.1097/00000542-200004000-00024 (2000)
**[2]** NMDA antagonist. Inventors: Franks and Maze US Patent number: 6274633
**[3]** Anaesthetic formulation comprising an NMDA-antagonist and an alpha-2 adrenergic agonist. Inventors: Franks and Maze US Patent number: 6562855
**[4]** Wilhelm S, Ma D, Maze M, Franks NP. Effects of xenon on in vitro and in vivo models of neuronal injury. *Anesthesiology* **96**:1485-91 DOI: 10.1097/00000542-200206000-00031 (2002)
**[5]** Ma D, Wilhelm S, Maze M, Franks NP. Neuroprotective and neurotoxic properties of the 'inert' gas, xenon. *British Journal of Anaesthesia* **89**:739-46 https://doi.org/10.1093/bja/89.5.739 (2002)
**[6]** Ma D, Yang H, Lynch J, Franks NP, Maze M, Grocott HP. Xenon attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. *Anesthesiology* **98**:690-8 DOI: 10.1097/00000542-200303000-00017 (2003)
**[7]** Ma D, Hossain M, Chow A, Arshad M, Battson RM, Sanders RD, Mehmet H, Edwards AD, Franks NP, Maze M. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. *Annals of Neurology* **58**:182-93 DOI: 10.1002/ana.20547 (2005)
**[8]** Lockwood GG, Franks NP, Downie NA, Taylor KM, Maze M. Feasibility and safety of delivering xenon to patients undergoing coronary artery bypass graft surgery while on cardiopulmonary bypass: phase I study. *Anesthesiology* **104**:458-65 DOI: 10.1097/00000542-200603000-00012 (2006)

**4. Details of the impact** (indicative maximum 750 words)

**Industry investment and commercialisation**
Shortly after the initial discovery that xenon was an inhibitor of NMDA receptors, Air Products inc. in July 2000 invested £750,000 in the formation of a spin-out company Protexeon Ltd. This company, through the work of the Imperial College Co-Founders, Professors Franks and Maze, developed the intellectual property portfolio that underpinned the subsequent clinical development of xenon as a neuroprotectant. In total, eight distinct patent families were developed.

In 2014 a new company, Neuroprotexeon Ltd. **[A]** was incorporated in the UK and £1.9 million raised in an initial round of funding, and an additional £3.2 million raised in a subsequent funding round. Professors Franks at Imperial College served as a Director, and chaired the Scientific Advisory Board of this new company. In 2015 the company entered into a twelve-year exclusive contract with Praxair Inc. for pharmaceutical grade xenon. Praxair is the largest industrial gas company in the Western Hemisphere, and one of only a handful able to produce clinical grade xenon **[B]**. In 2016, the company formed a strategic partnership with Penlon Ltd., a medical device company, to advance the development and production of an in-hospital adult xenon delivery device **[B]**.

In 2017 the company entered into a licensing agreement with Mallinckrodt plc for the development and commercialisation of pharmaceutical-grade xenon gas for inhalation therapy. Specifically, for xenon to be evaluated to improve survival and functional outcomes for patients resuscitated after a cardiac arrest. This provided $10 million in up-front and up to $25 million in milestone payments **[C]**, together with tiered net-sales-based royalties, to reimburse Neuroprotexeon for product development costs, in exchange for exclusive rights to commercialise the therapy in the USA, Japan and Australia **[C]**.

In 2018, Neuroprotexeon entered into a partnership with Linde plc, to aid in the development of xenon to treat Post Cardiac Arrest Syndrome for the European Union plus United Kingdom, Switzerland, Norway and Iceland **[D]**. This agreement provided a further £20 million plus tiered royalties. Sudden out-of-hospital cardiac arrest is the third leading cause of death in industrialised countries. The EuReCaONE study **[E]** of 27 EU countries showed the incidence of out-of-hospital

cardiac arrest is as many as 84 per 100,000 population, suggesting that c.426,000 patients could be affected across the EU every year.

Neuroprotexeon has established a favourable regulatory position having secured Fast Track status and Special Protocol Assessment from the FDA (US Food and Drug administration) for the Phase III trial (see below), as well as orphan drug status from both the FDA and the EMA (European Medicines Agency).

**Clinical trials**

The first clinical trial was carried out at Imperial College to test the safety and feasibility of delivering xenon to patients undergoing coronary artery bypass grafting surgery **[F]**. Xenon was delivered to 16 patients throughout surgery using both a standard anaesthetic breathing circuit and an oxygenator. This study concluded that xenon could be safely and efficiently delivered to coronary artery bypass grafting patients while on cardiopulmonary bypass. A second trial, funded by the Medical Research Council (UK) **[G]**, investigated the possible use of xenon, combined with hypothermia, to treat perinatal asphyxia **[H]**. Both trials showed that xenon could be safely delivered to patients, but evidence for efficacy was lacking.

In 2015, the results **[I]** from the first Phase II trial testing the efficacy of xenon combined with hypothermia to treat 110 comatose patients who had experienced out-of-hospital cardiac arrest. The primary end point was cerebral white matter damage as evaluated by fractional anisotropy from diffusion tensor MRI, performed between 36 and 52 hours after cardiac arrest. Among comatose survivors of out-of-hospital cardiac arrest, inhaled xenon combined with hypothermia compared with hypothermia alone resulted in significantly less ($P$ = 0.006) white matter damage as measured by fractional anisotropy of diffusion tensor MRI.

These results were important in obtaining FDA and EMA approval for a Phase III trial **[J]** to determine if xenon combined with hypothermia was efficacious in treating brain injury following cardiac arrest. This is a prospective, randomized, multicenter interventional trial in adult subjects with out-of-hospital cardiac arrest comparing treatment with standard-of-care post-cardiac arrest intensive care (targeted temperature management [TTM]), to xenon by inhalation plus standard-of-care post-cardiac arrest intensive care (including TTM). The trial recruited its first patient in December 2018 **[J]**.

**Potential for clinical benefit**

There are no effective treatments for neurological injuries following trauma, stroke or hypoxia. Because similar injury pathways are thought to occur, a demonstration that xenon was efficacious in the cardiac arrest Phase III trial would give tremendous impetus to the use of xenon in other settings. Moreover, where no existing treatments exist, even small benefits can result in a treatment being widely adopted, resulting in great clinical impact.

**5. Sources to corroborate the impact** (indicative maximum of 10 references)

**[A]** Companies house https://find-and-update.company-information.service.gov.uk/company/09202593/filing-history?page=3 (Archived here)

**[B]** Partnerships https://www.neuroprotexeon.com/npxe/partners/ (Archived here)

**[C]** https://www.mallinckrodt.com/about/news-and-media/news-detail/?id=8656 (Archived here)

**[D]** https://www.prnewswire.com/news-releases/european-distribution-partnership-between-neuroprotexeon-and-linde-300644969.html (Archived here)

**[E]** EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Gräsner JTet al. Resuscitation. 2016 105:188-95. DOI: 10.1016/j.resuscitation.2016.06.004 (Archived here)

**[F]** Lockwood GG, Franks NP, Downie NA, Taylor KM, Maze M. Feasibility and safety of delivering xenon to patients undergoing coronary artery bypass graft surgery while on cardiopulmonary bypass: phase I study. Anesthesiology 104:458-65 (2006) DOI: 10.1097/00000542-200603000-00012 (Archived here)

**[G]** MRC Clinical Trial "Neuroprotective effect of hypothermia combined with inhaled xenon following perinatal asphyxia" (£1,088,610) (Oct 2010 - March 2014) Azzopardi (PI) (with Franks, Maze, Hajnal, Cady & Robertson) https://gtr.ukri.org/projects?ref=G0701714 (Archived here)

**[H]** Azzopardi D, Robertson NJ, Bainbridge A, Cady E, Charles-Edwards G, Deierl A, Fagiolo G, Franks NP, Griffiths J, Hajnal J, Juszczak E, Kapetanakis B, Linsell L, Maze M, Omar O, Strohm B, Tusor N, Edwards AD. Moderate hypothermia within 6 h of birth plus inhaled xenon versus moderate hypothermia alone after birth asphyxia (TOBY-Xe): a proof-of-concept, open-label, randomised controlled trial. Lancet Neurology 15:145-153 (2016) DOI: https://doi.org/10.1016/S1474-4422(15)00347-6 (Archived here)

**[I]** Laitio R, et al. Effect of Inhaled Xenon on Cerebral White Matter Damage in Comatose Survivors of Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial Journal of American Medical Association 315:1120-8 (2016) DOI: 10.1001/jama.2016.1933 (Archived here)

**[J]** https://clinicaltrials.gov/ct2/show/NCT03176186 (Archived here)