MARIE SKLODOWSKA-CURIE ACTIONS
Co-funding of regional, national and international programmes (COFUND)

DOC2AMU THESIS PROJECT 2018 CALL FOR APPLICATIONS

Studies for improved recovery, measurement and recycling of xenon in clinical anaesthesia

1. GENERAL INFORMATION

Call 2018-15
Topic Nano-health
Keywords Nanoporous adsorbents, cryptophanes, xenon, anaesthesia, ultrasonic gas analysis, xenon recycling

2. THESIS DIRECTOR(S), RESEARCH UNITS AND DOCTORAL SCHOOLS

Thesis director Alexandre MARTINEZ
Research Unit Institut des Sciences Moléculaires de Marseille
Doctoral school ED 250 - Sciences Chimiques
Thesis co-director Gregory HALLEWELL
Research Unit Centre de Physique des Particules de Marseille
Doctoral school ED 352 - Physique et Sciences de la Matière
1. DESCRIPTION OF THE PHD THESIS PROJECT

1.1 OBJECTIVES OF THE PROJECT BASED ON THE CURRENT STATE OF THE ART

The objective of the project is to help widen the benefit to patients from an increase in the number of possible xenon anaesthesia operations through better monitoring and post-operative recovery and recycling of xenon.

Xenon (molecular weight 131) is the heaviest non-radioactive noble gas and the only noble gas displaying anaesthetic properties at ambient pressure. It combines almost ideal anaesthetic properties - including fast onset and emergence - with minimal side effects. It causes no depression of blood pressure or myocardial contractility and is a possible organ protectant. It is not metabolized and so emerges from the lungs unchanged at the end of an anaesthetic [1]. When combined with patient cooling it has shown promise as a neuroprotectant against hypoxic-ischemic brain injury [2], and also as a myocardial protectant [3]. The anaesthetic potential of xenon has been recognized since the 1950’s. It was first approved as an anaesthetic in Russia in 2002 [4] and has also gained licences for use in Europe as LENOXe™ (manufacturer: Air Liquide, France). Xenon is present in air at a concentration of $8.7 \times 10^{-8}$. Its separation is energetically uneconomic unless part of a cascade for more common gases with wide industrial usage. Worldwide production of xenon in 2007 was around 15 million litres. In contrast with many other anaesthetic gases and vapours, xenon release does not degrade the environment or contribute to global warming. There are however strong arguments for recycling since the high cost of medically-approved xenon (around $30/litre) is limiting its use and its potential benefits to patients.

Despite its slow uptake by the human body (around 3 l/hr), its much higher cost - compared with other inhalation anaesthetics - predicates its use either in true “fully-closed” circle breathing circuits or in “semi-closed” circuits equipped to recover xenon (from a slight excess of gas) lost through an “overspill” valve during an anaesthesia. The cost per operation could be further reduced - and the possible number of operations further increased - through improved monitoring of xenon concentration in the breathing gas mixture and also during post-operative gas recovery from the breathing circuit and also from the patient.

Prior studies on the recovery of anaesthetic xenon for reprocessing have centred on trapping in zeolites [5] cooled with liquid nitrogen (LN$_2$), and on the “desublimation” of xenon onto a cooled copper surface at -139 °C in a prototype system [6]. We consider that xenon reprocessing from enriched clinical sources could become energetically favourable and cost-competitive with the present condensation of xenon from air, through the use of modern nanoporous adsorbents exhibiting a high selectivity and adsorbance for xenon, while operating at more easily-achievable temperatures of -20 °C or above.

This PhD project will combine a study of the adsorption and recovery of xenon in modern nanoporous materials together with the development of improved ultrasonic instrumentation for the measurement of xenon concentration in breathing gas mixtures. The proposal contains complementary activities with collaborators.
The project objectives, discussed in more detail in §1.2 are:

- the development of improved ultrasonic instrumentation for simultaneous flowmetry and sub-% precision measurements of xenon in circulating and recovered anaesthetic gas mixtures;
- the identification of modern cost-effective nanoporous adsorbers that will efficiently and selectively capture xenon at warmer temperatures more easily achieved than in [5] and [6];
- trials with an anaesthesia delivery machine circulating Xe/O\(_2\) mixtures under “fully-closed-circle” and “semi-closed circle” protocols will measure the consumption of xenon and the amount recovered in different adsorbents;

Once promising nanoporous materials have been identified an approach will be made to industry in an effort to develop a feasibility-cost model for introducing recycled xenon into the clinical xenon supply chain: including the value of recovered gas, initial cost of adsorbents, handling costs for xenon recovery, repeated adsorbent reactivation and repackaging for reuse.

A recently-approved clinical trial using xenon for neuroprotection during post-cardiac arrest syndrome in comatose survivors of out-of-hospital cardiac arrest (https://clinicaltrials.gov/ct2/show/NCT03176186) ("XePOHCAS") will take place with more than 1400 patients in multiple hospitals in the US. The likely duration of 50%Xe/50%O\(_2\) ventilation will be 24 hours in this study. Should the study pave the way for xenon post-cardiac arrest treatment in intensive care units, economical means of delivering, monitoring and recycling anaesthetic xenon will become extremely relevant to future practice and the expansion of the benefits of xenon anaesthesia and/or neuroprotection.

Keywords: Nanoporous adsorbents, cryptophanes, xenon, anaesthesia, ultrasonic gas analysis, xenon recycling

1.2 METHODOLOGY

The thesis project hinges on 3 complementary activities to be followed with collaborators at 3 partner institutes.

(1) Improved ultrasonic instrumentation for simultaneous flowmetry and Xe-O\(_2\) gas mixture analysis

Binary gas mixture and flow can be simultaneously measured in a single instrument via pulse transit timing in opposite directions in flowing gas The transit time difference is proportional to the flow while the average can be used with a stored look-up table of concentration vs. sound velocity of the two components over a range of temperature and pressure spanning the expected conditions to obtain the concentrations of the components. This activity is a continuation of research carried out by Dr. Hallewell [7]-[9]: one of the two supervisors. Ultrasonic measurements will be made at Aix-Marseille Université - Centre de Physique des Particules de Marseille (AMU-CPPM) and also in collaboration with Professors John Dingley and David Williams at the Department of Anaesthetics, Morriston Hospital, University of Wales, UK, who have made numerous developments in anaesthesia instrumentation, including an Arduino-Python-based readout system for an adapted medical ultrasonic flowmeter [10]. The new ultrasonic instrumentation is intended to improve the precision of xenon delivery during anaesthesia and help reduce wastage in the post-operative environment where xenon is recovered for recycling. Figure 1 illustrates the working principle of such an instrument together with sound velocity in varying mixtures of Xe and O\(_2\). The precision of Xe-O\(_2\) mixture determination \(\delta m\), depends on the uncertainty in the measurement of the sound velocity, \(\delta c\), and on the local slope of the sound velocity/concentration curve, \(\alpha\), at the process gas temperature and pressure according to \(\delta m = \delta c / \alpha\). Typical sound velocity measurement uncertainties in the instruments developed by the supervisor’s group so far are in the range 0.025 - 0.05 ms\(^{-1}\) [7]-[9]. In mixtures of xenon with O\(_2\) the average slope over the full clinical range from 0-70% Xe is around -1.7 ms\(^{-1}\) [% Xe\(^{-1}\)]; a sound velocity measurement uncertainty of 0.05 ms\(^{-1}\) would yield a Xe-O\(_2\) mixture measurement uncertainty of ± 3.10\(^{-4}\).
Figure 1: (a, b) Working principle of a combined ultrasonic flowmeter and binary gas analyser with (c) an example of sound velocity variation in Xe-O₂ anaesthetic gas mixtures.

(2) Improved techniques for xenon capture on modern nano-porous materials

This activity will follow on from molecular cage research of Prof. Alexandre Martinez of AMU – Institut des Sciences Moléculaires de Marseille (AMU-ISM2): the 1st supervisor, and from the work carried out on radon trapping by our collaborator Prof. Jose Busto at AMU-CPPM. We will exploit the almost identical atomic radii (and probable trapping characteristics) of $^{222}\text{Rn}$ and $^{131}\text{Xe}$, allowing small adsorbent samples to be first characterized with $^{222}\text{Rn}$ in an improved test stand at AMU-CPPM before larger samples of promising candidates are subjected to chemisorption studies at AMU-ISM2. Examples of studies carried out on the characterisation of $^{222}\text{Rn}$ adsorbents are given in [11] & [12]. It is possible to exploit the radioactivity of $^{222}\text{Rn}$ in this first step to retain or eliminate adsorbents based the change in activity measured in gas upstream and downstream of small adsorbent samples. These small-scale initial tests can be made more easily with higher precision with a $^{222}\text{Rn}$ tracer than with xenon. Follow-up tests in larger samples of the selected materials are detailed below.

This study aims to identify highly-selective xenon adsorbents operating as close to room temperature as possible. Cryptophanes are one of the rare class of host molecules capable of selectively complexing $^{131}\text{Xe}$ and $^{222}\text{Rn}$ with a high binding constant $>10^4$ [13] - [15], and could be ideal candidates to efficiently trap xenon at room temperature (by physisorption or covalent link). The kinetics of exchange is slow on NMR timescales, suggesting that xenon should be trapped more efficiently at warmer temperature than in zeolites and other types of molecular sieves. Tailoring the size and shape of the cavity should allow the kinetics of the host-guest exchange to be tuned to allow xenon complexing at the desired temperature. Such complexation is reversible, allowing xenon to be released (through a simple industrial procedure with temperature increase or a nitrogen purge, for example) when required for the adsorbent to be easily recycled. Cryptophane cages will be synthesised and “grafted” onto support materials to make structures that will be very stable under the conditions to be encountered in this project. Adsorption capacity and xenon selectivity will then be measured as a function of adsorbent temperature and concentration in a carrier gas including oxygen. With these campaigns of adsorption measurements we aim to identify cost-effective nanoporous xenon adsorbers that will effectively capture xenon on at temperatures more easily achieved than in [5] and [6].

(3) Measurements with an anaesthesia delivery machine with circulating and recovered Xe/O₂ mixtures

Trials with an anaesthesia delivery machine circulating Xe/O₂ mixtures will be made under “fully-closed-circle” and “semi-closed circle” protocols to measure the consumption of xenon and the amount recovered in different adsorbents. These trials will be carried out in collaboration with Profs Dingley and Williams at Morriston Hospital, UK. These trials will make use of the improved ultrasonic instrumentation developed in the same project for measurement of xenon concentration in the circulating mixture and in all waste gases for xenon consumption measurements. The metabolism of O₂ to CO₂ may be studied using a combustion “simulated lung” [16].

Co-supervision during the duration of the project will be provided by Prof. Martinez, Dr. Hallewell and Profs Dingley and Williams during the periods spent by the candidate at their respective institutes. Regular contacts between the supervisors as well as progress reviews and reports are foreseen during the duration of the project.
1.3 WORK PLAN

A detailed time line with the inter-relations between the principal supervised activities during the 3 year timescale of the PhD is shown as a chronogram. The major activities are colour coded: ultrasonic studies (yellow); synthesis of cage molecules, their grafting on supports and characterization through chemical adsorption studies (green); measurements in gas mixtures in an anaesthesia circuit and following recovery from the circuit (beige). Also shown are proposed concurrent managerial and outreach activities related to cultivation of future industrial opportunities, and - following sufficient advancement of the adsorption studies – the aim to determine a cost-feasibility model in conjunction with industry for the recycling of medical xenon and adsorbents.

1.4 SUPERVISORS AND RESEARCH GROUPS DESCRIPTION

Prof. A. Martinez (AMU-ISM2), 1st supervisor (thesis director): St Jerome: synthesis of the molecular cages for trapping Xe; measurements of adsorption and co-adsorption of Xenon, with Dr. T. Brodin and J.-P. Dutasta (Ecole Normale Superieure, Lyon) for Xe complexation and with Dr. V. Dufaud (Ecole Superieure de Chimie Physique Electronique, Lyon) for the synthesis and characterization of materials. See also §2.1 & §5.1.

Dr. G. Hallewell (AMU-CPPM), 2nd supervisor (thesis co-director): ultrasonic measurements and the building of a prototype instrument with firmware and the cell holder/flowcell, with Prof. J. Busto: supervising pre-characterisation measurements of nanoporous adsorbers at CPPM, based on the similar dimensions of $^{131}$Xe and $^{222}$Rn atoms*. See also §2.1, §5.2 & §5.3.

Profs J. Dingley and D. Williams, Department of Anaesthetics, Morriston Hospital, Swansea, Univ. Wales, international and intersectorial collaborators: measurements of xenon recovery with selected adsorbents using an anaesthesia delivery machine operating in “fully-closed circle” and “semi-closed circle” modes. Also the development of related instrumentation [6], [10]; see also §2.1 & §5.4.

*We have received notification (October, 2017) that we will receive 21 200 Euros for equipment purchase from the “Apex 2017” appel à projets grant of the Region Provence-Alpes-Cote d’Azur for the project “Rexan: Développement d’un dispositif de récupération et contrôle de Xénon pour l’anesthésie” (Busto, Hallewell). These funds will be spent on materials for the improvement of a test bench currently at AMU-CPPM to measure $^{222}$Rn trapping on nanoporous materials, and for the construction of a new test bench for the measurement of xenon capture from mixed gas streams in nanoporous adsorbents. This test bench will incorporate new ultrasonic instrumentation. These funds are not awarded for the support of personnel.
2. 3I DIMENSIONS AND OTHER ASPECTS OF THE PROJECT

2.1 INTERDISCIPLINARY DIMENSION

The skills of the proposed supervisors and their collaborators are complimentary in the context of a project to evaluate improvements in recovery, measurement and recycling xenon in clinical anaesthesia. All are experts in their respective domains: at the University of Wales, Swansea in xenon anaesthesia; at the two AMU institutes in organic synthesis, supramolecular chemistry, materials and physical chemistry and ultrasonic gas analysis.

Profs J. Dingley and D. Williams, Department of Anaesthetics, Morriston Hospital, Swansea, Univ. Wales, supervision of the candidate in “bench study” measurements of xenon recovery with selected adsorbents using an anaesthesia delivery machine operated in “fully-closed circle” and “semi-closed circle” modes at Swansea.

Prof. A. Martinez (AMU-ISM2): supervising synthesis of the molecular cages for trapping Xe; and of the PhD candidate in measurements of adsorption and co-adsorption of Xenon: also with Drs. T. Brotin and J.-P; Dutasta (Ecole Normale Superièure, Lyon) for Xe complexation and Dr. V. Dufaud (Ecole Superièure de Chimie Physique Electronique, Lyon) for the synthesis and characterization of materials.

Dr. G. Hallewell (AMU-CPPM): supervising ultrasonic measurements and the building of a prototype instrument with firmware and the cell holder/flowcell, with Prof. J. Busto: supervising pre-characterisation measurements of nanoporous adsorbers at CPPM, based on the similar dimensions of $^{131}$Xe and $^{222}$Rn atoms.

2.2 INTERSECTORAL DIMENSION:

The intersectorial partner in the field of health care is the Department of Anaesthetics of Morriston Hospital, University of Wales, Swansea, UK, where Profs Dingley and Williams are renowned experts in the use of xenon for clinical anaesthesia and in the development of related recuperation techniques and instrumentation [6], [10].

The candidate will participate in Xenon recuperation measurements using an anaesthesia gas delivery machine operating in “fully-closed circle” and “partially-closed circle” under simulated respiratory conditions. Visits to the Department of Anaesthetics, Morriston Hospital for studies with an anaesthesia delivery system are foreseen as part of this PhD work program. Participation in tests and presentations by the candidate at regular progress meetings is expected at the collaborating institutes, making use - as necessary - of videoconferencing tools.

We believe that the project could contribute to addressing the following SR1-S3 objective of the PACA region: “Transition and energy efficiency”. While the main aim of the project is wider benefit-to-patients via an increase of the number of xenon anaesthesia operations through better monitoring and post-operative recycling of xenon, the recycling of post-operative gas already rich in xenon could offer energy gains in the production of xenon. Also the replacement of even a small fraction of the currently-used anaesthetics, including nitrous oxide (N$_2$O), sevoflurane and other halogenated anaesthetics, will contribute to reducing emissions of anaesthetic gases with a high global warming potential.

2.2 INTERNATIONAL DIMENSION:

The project has a dynamic international dimension. Prof. Dingley and Prof. Williams of the Department of Anaesthetics, Morriston Hospital, University of Wales, Swansea, UK are renowned experts in the use of xenon for clinical anaesthesia and in the development of related instrumentation. In addition to studies carried out at CPPM Profs Dingley and Williams have made several detailed studies of ultrasonic analysis of xenon/oxygen gas mixtures as indicated in the section on recent publications. Participation of the doctoral candidate in international conferences related to xenon anaesthesia is to be expected during the duration of the PhD project.
3. RECENT PUBLICATIONS

3.1 Short selection of relevant xenon anaesthesia and recovery references


4. EXPECTED PROFILE OF THE CANDIDATE

The candidate should have a master’s degree in applied physics or an engineer diploma in instrumentation, preferably related to gas systems and fluidics, or an engineer diploma from a general engineer school. S/he should ideally combine an interest in the physics and chemistry of gaseous adsorption in molecular cages and nanoporous materials with an interest in applied physics as it relates to the analysis of gas mixtures and flowmetry. A practical interest in instrumentation would be an advantage: the project will offer opportunities requiring the development of readout systems using microcontroller-based electronics, based (for example) on Arduino or Raspberry Pi implementations. An interest in programming in Python is required. The project will also offer opportunities for the analysis of fluid flow using modern computational fluid dynamic packages and also in the 3-D design of ultrasonic flow cells using modern 3-D design software such as Catia3-D. Participation in significant measurement campaigns in adsorptivity and ultrasonic analysis of Xenon-Oxygen gas mixtures in Marseille and Swansea is expected. Participation and presentations in regular progress meetings is expected at the collaborating institutes, making use - as necessary - of videoconferencing tools. Knowledge and basic skills in organic chemistry and chemistry of materials would be also highly appreciated, allowing the candidate to understand the synthesis of molecular cages and their support on materials. It should be noted that the synthesis of some molecular cages capable of Xe complexation has been already reported and new syntheses would normally be performed by the chemists involved in this consortium, helping make the interdisciplinary aspect of this PhD project realistic.

5. SUPERVISORS’ PROFILES

5.1 First Supervisor

Alexandre Martinez, AMU Institut de Sciences Moleculaires de Marseille, Service 462, Campus Scientifique de St Jérôme, Marseille Cedex 20 (AMU-ISM2)

Prof. Martinez obtained his PhD in 2004 under the supervision of Dr. B. Meunier (LCC Toulouse). After a post-doc position in the group of J. Lacour (University of Geneva), he obtained a position of associate professor at Ecole Normale Superieure (ENS) Lyon in the team of J.-P. Dutasta and obtained his Habilitation à Diriger des Recherches from ENS Lyon in 2013. In 2014, he became a professor at the Ecole Centrale de Marseille, where he continues research initiated at ENS Lyon related to new aspects of hemicryptophane. He focuses on host-guest recognition, and catalysis in confined spaces. He leads the Chirosciences team (18 permanent researchers) and has authored or co-authored around 75 scientific works (63 in peer reviewed journals). A short CV and a complete list of publications is available at: [http://ism2.univ-amu.fr/fr/annuaire/chirosciences/martinezalexandre](http://ism2.univ-amu.fr/fr/annuaire/chirosciences/martinezalexandre)

Prof. Martinez’s principal expertise is in supramolecular chemistry; in particular in covalent cages based on the cyclotriveratrylene unit (cryptophanes and hemicryptophanes) and the study of their recognition properties. He has also extensive knowledge in materials chemistry and maintains a network of collaborators at national and international levels (5 and 8 respectively, please see web site above for the complete list) including a collaboration with Dr. Véronique Dufaud (CPE Lyon), which can be of benefit to this project. These fruitful collaborations have led to common publications and highlight his ability to interact with other research groups: a key point for the future development of this activity.

**Supervision of PhD students**

Prof. Martinez has supervised 7 completed PhD theses (start year; duration; number of articles related to the thesis; current position): P. Dimitrov-Raïtchev (2011; 3 yrs; 8 art.; responsible for links between industry and University, Université Claude Bernard, Lyon 1), O. Perraud (2012; 3 yrs; 12 art.; teacher), B. Chatelet (2013, 3 yrs;
Current PhD supervision:

J. Zhang (01/10/2015-01/10/2018), F. Lagarde (01/10/2015-01/10/2018), M. Delecluse (01/11/2015-01/11/2018), R. Membrat (01/10/2016-01/10/2019), A. Long (01/10/2016-01/10/2019), G. Qiu (01/10/2017-01/10/2020)

5.2 Second Supervisor

Gregory HALLEWELL, Aix Marseille Univ, CNRS/IN2P3, CPPM, Marseille, France (AMU-CPPM)

Dr. Hallewell (orcid.org/0000-0001-6267-8560) received a PhD in Particle Physics in 1982 and a Habilitation à Diriger des Recherches from the Université Aix-Marseille in February 2011. He is employed at the Centre de Physique des Particules de Marseille as an Ingénieur de Recherche H.C. in instrumentation (CNRS-IN2P3). Since 2009 he has led the Inner Detector (“IDE”) Sonar project - which has involved a team that peaked at around 20 scientists, engineers and technicians in 2015 and is now around 5 people - of the ATLAS experiment at the CERN Large Hadron Collider. The group has developed custom microcontroller-based ultrasonic instrumentation for simultaneous analysis and flowmetry of a variety of gas mixtures used within the ATLAS inner detector (IDE) and has integrated this into the hardware and software of the ATLAS detector control system ([7] – [10] & § 3). Prior to joining CPPM in 1991 Dr. Hallewell had been a Postdoctoral researcher (1985-89) and Staff physicist (1989-1991) at the Stanford Linear Accelerator Center, Stanford University, California, USA. He has also been seconded from CPPM as a visiting scientist at the Rutherford Appleton Laboratory, Chilton, UK (2000-2001) and as an invited scientific associate at CERN (1998-2000), on the ATLAS-LHC experiment. He has been a leader in the field of ultrasonic gas analysis in particle physics applications since the 1980s, his research having been carried out at Stanford, and currently at AMU-CPPM (CNRS) and at CERN.

Co-Supervision of PhD students (as part of their authorship qualification tasks in the ATLAS-LHC Collaboration)

Dr Hallewell has advised 5 PhD students on the sections of their PhD theses dedicated to the ATLAS IDE_sonar system: M Doubek (Czech Technical Univ. Prague 2015-8), A. O’Rourke (Manchester Univ. 2014-7), B. Pearson (Oklahoma Univ. 2013-6), A. Bitadze (Glasgow Univ.: 2010-3) and N. Bousson (Aix-Marseille Univ. 2009-2012). Three IUT students (R. Vaglio, N. Langevin and J. Berthoud) have completed part of all of their thesis/dissertation work in the ATLAS IDE_sonar group. The group (currently around 5 persons) is very active in publication, counting 22 journal papers and conference proceedings papers since 2011, with 18 presentations so far at international conferences and workshops, the most recent being the prestigious ICALEPCS2017 conference in Barcelona in October 2017. Priority is given by the group for conference participations by students and younger personnel without permanent contracts.

Relevant peer-reviewed papers with PhD students as communicating authors


A. O’Rourke recently completed her PhD at Manchester University (2014-2017)


B. Pearson is currently a post-doctoral researcher at the Max Planck Institute for Physics, D-80805 Munich Germany, currently working on the CERN ATLAS LHC experiment


A. Bitadze (PhD 2010-2013) is currently a post-doctoral researcher at Manchester University, UK, currently working on the CERN ATLAS LHC experiment


Presented by M. Doubek at the 14th International Conference on Accelerator and Large Experimental Physics Control Systems (ICALEPCS2013), San Francisco, USA (October 6-13, 2013)

M. Doubek is currently in the final year of his PhD (2013-2018) at the Czech Technical University in Prague, currently working on the CERN ATLAS and TOTEM LHC experiments.

**Supervision for rapports fin d'études (dépts de mesures physiques, IUT Annecy & IUT St. Jerome, Marseille)**

(1) “Analyse de mélanges de gaz par vitesse de so dans le context du réfroidissement du tracker silicium ATLAS”; rapport fin d’études: Romain Vaglio, IUT Annecy ; June 2015

(2) “Etude d’un débitmètre/analyseur de gaz par ultrasons”; rapport fin d’études: Nicolas Langevin, IUT St. Jerome, Marseille, June 2012

(3) “Mise en oeuvre d’un débitmètre et d’un analyseur de mélanges gazeux”; rapport fin d’études: Jonathan Berthoud, IUT Annecy ; June 2012

No PhD students are currently being supervised (November 2017). Dr. Hallewell expects to take on a student for stage de fin d’études (IUT St Jerome, Marseille, April-June 2018)

**5.3 Participation of Prof José Busto (AMU-CPPM), collaborator of Dr. Hallewell:**

Prof. Busto (AMU-CPPM) is a physicist who has developed a test stand to measuring the efficiency of capture of $^{222}$Rn on nanoporous materials as a function of temperature, pressure and carrier gas [11], [12]. Construction of a second test stand for adsorption studies at flows characteristic of xenon recovery from anaesthesia is foreseen for his laboratory using funds to be received under the “Apex 2017” appel à projets grant of the Region Provence-Alpes-Cote d’Azur. These facilities will be used in the context of this PhD research project. At the start of the project, before the arrival of the first cryptophanes, Prof. Busto will first test the new facilities using materials (various types of active carbon or carbon-based molecular sieves, including Carbosieve SIII) that he has found to be efficient adsorbers of $^{222}$Rn.

**5.4 Participation of Profs. John Dingley and David Williams**

Profs. Dingley and Williams are internationally-recognised experts in the field of Xenon anaesthesia, and in the development of related technology, with extensive contacts with suppliers of anaesthesia equipment and gases. They are consultant anaesthetists at Morriston Hospital, Swansea; the University teaching hospital linked to
Swansea University Medical School. They will coordinate trials using an anaesthesia machine operated in “fully-closed cycle” and “semi-closed cycle” modes with xenon motoring and recovery at the end of each simulated anaesthesia. Experiments will include tests of the recovery of xenon from the final gas stream with ultrasonic instrumentation upstream and downstream of the adsorbent cartridges. Less expensive industrial xenon can be used in these tests, with metabolic \( \text{O}_2 \rightarrow \text{CO}_2 \) transformation possibly simulated by a flame. They may be assisted in these studies also through additional facilities provided by Dr. Peter Douglas of Swansea University Chemistry Department. Profs Dingley and Williams will act as international secondment tutors to the successful candidate for this project. At least one meeting or conference calls every two weeks will be organised with the AMU supervisor during the candidate’s secondment period to assess his/her research and training progress. Short minutes of these meetings will be included in the fellow’s annual report.

5.5 Participation of Drs. T. Brotin, J.-P Dutasta and V. Dufaud (collaborators of Prof. Martinez)

Drs. T. Brotin and J.-P. Dutasta are world leaders in the chemistry of cryptophanes, and demonstrate that small neutral molecules like Xenon can be encapsulated in the molecular cavity of these molecular hosts.

Dr. V. Dufaud is a Senior CNRS Researcher who recently joined the catalysis and polymerization Laboratory (C2P2) at CPE-Lyon. She develops novel integrated approaches to the design of multifunctional catalytic materials showing high activity and selectivity. Her current interest focuses on the development of catalytic solids with enhanced performance via SOMC and materials science approaches. Thus, her participation is necessary for the immobilization of the cages.
AVIS DES DIRECTEURS DES LABORATOIRES CONCERNES PAR LE PROJET DE THESE

Avis du directeur du laboratoire du directeur de thèse, M. NOM Prénom

☐ Favorable  ☐ Défavorable

Commentaires :

Fait à Marseille, le 02/01/2018

Signature

Cristinel DIACONU
Directeur du CPPM

CENTRE DE PHYSIQUE DES PARTICULES DE MARSEILLE
CNRS/IN2P3 - Aix-Marseille Université
163, Avenue de Luminy - Case 902
13288 Marseille Cedex 9
Tél. : 04 91 82 72 00 - Fax : 04 91 82 72 99

Avis du directeur du laboratoire du co-directeur de thèse, M. NOM Prénom

☐ Favorable  ☐ Défavorable

Commentaires :

Fait à Marseille, le 21/12/2017

Signature
6th January 2018

Tommaso Zaccaro,
Ingénieur – Manager de Projets Européens,
Protisvalor - Filiale de Valorisation d’Aix-Marseille Université,
5-9 Boulevard Maurice Bourdet, CS 80501,
13205 Marseille Cedex 01, France

Dear Mr. Zaccaro,

Re: DOC2AMU THESIS PROJECT 2018 CALL FOR APPLICATIONS
Studies for improved recovery, measurement and recycling of xenon in clinical anaesthesia.

I would be very pleased, with my colleague Dr David Williams, to act as an International secondment tutor to the successful candidate for this project. As described more fully in the application, this would involve a series of bench studies simulating the clinical delivery of xenon anaesthesia, with evaluation and cost analyses of the proposed novel means of selective xenon recovery from waste gases.

At least 1 meeting or conference calls every two weeks will be organised with the AMU supervisor during this secondment period to assess the PhD student’s research and training progress. Short minutes of these meetings will be included in the fellow’s annual report.

Yours sincerely

John Dingley FRCA MD
Associate Professor of Anaesthetics
Consultant Anaesthetist