



Science and  
Technology  
Facilities Council



# STFC Central Laser Facility

How to Apply for Access to the CLF

SAQN Training Day

# The start....

- An idea for an experiment that requires, or could greatly benefit from, a laser-based technique.
- Blue-sky, off-the-wall, left-field
- Part of your research programme
- Before going any further - discuss with a facility scientist at the CLF!!
- To find that person wrt SAQN applications talk to me, Sarah or Fleur



# Potential Techniques

- Aerosol droplet analysis
- Raman micro-spectroscopy
- Laser microscopy for imaging
- Spatially offset Spectroscopy
- Kerr gated and NIR Raman spectroscopy
- Flash Radiography
- Ptychography



## **Central Laser Facility *Octopus* and *Ultra* facilities:** **Call for access**

**Period:** Access from July 2022 to December 2022

**Deadline:** 17:00 GMT (PROMPT) Tuesday 18<sup>th</sup> January 2022

**Access mode: Direct Access and Approved Programmes:** *Octopus* and *Ultra*

**Access Mode: New programme access:** *Octopus* and *Ultra*

**Access Mode: EU Direct Access (Laserlab-Europe):** *Octopus* and *Ultra*

**Please carefully read all the information below before submitting an application. Failing to follow the guidelines below may result in your proposal being returned without review.**

[Where to apply](#)

[Before applying](#)

[Types of access mode and guidance](#)

[Direct Access](#)

[New Programme Access](#)

[Continuing Programme Access](#)

[Proposal assessment criteria](#)

### **Where to apply**

Applications are made through the STFC online submission system, which can be found here:

<https://proposal.isis.rl.ac.uk/home>

**EU access** is provided through Laserlab Europe: <https://www.laserlab-europe.eu/>. Please check your eligibility at <https://www.laserlab-europe.eu/transnational-access/how-to-apply-for-access/criteria-of-eligibility-for-transnational-access>. You will need to submit your proposal to both STFC and Laserlab Europe. To do this:

- On the CLF proposal form, select Direct access route and answer yes when asked "Are you applying through Laserlab?" at Step #2 (Facility & Funding)

- Download a .pdf copy of your application and use the Laserlab online proposal system at <https://apply.laserlab-europe.eu/> to submit it
- Note that the Laserlab site asks for detailed information about your co-applicants, including their year of birth
- At the last step, attach the .pdf copy of your proposal produced by the CLF proposal system. The Laserlab site requires that your .pdf be less than 1 MB in size

Further information can be found under "Calls for access to Octopus and Ultra" on the Central Laser Facility website:

<https://www.clf.stfc.ac.uk/Pages/Access-to-Octopus-and-Ultra.aspx>

All applications are peer reviewed by a Facility Access Panel (FAP) comprising of UK and international academics.

### **Before applying**

**Applicants are strongly recommended to contact an appropriate CLF staff member to discuss requirements before applying, even if you have previously submitted a proposal.**

**Eligibility for access to *Octopus* and *Ultra* through this call:**

- 1) UK and EU academics: All academics, including those from Research Council institutes (including STFC staff) and those with Research Council senior or advanced research fellowships (or their equivalent) and Royal Society and Royal Academy of Engineering fellowships, will be eligible for access to the STFC facilities.
- 2) UK and EU Postdoctoral Researchers: Postdoctoral researchers from universities are eligible for access.
- 3) Applicants must hold a position that lasts for the duration of the above scheduling period.

### **Applicants to *Octopus* please note:**

*Octopus* offers access across all microscope systems (see brochure and website for further information on the techniques available).

- The facility operates with more than one user group simultaneously. All applicants **must** apply for sufficient access to cover the use of each microscope required. For example, a group intending to use two different *Octopus* microscopes simultaneously for one week on each should apply for two weeks of access. Applicants must include in their proposal a detailed breakdown of which *Octopus* microscopes they require, and the amount of time required on each. Proposals will be returned if this information is not provided.
- The guideline allocated time for programme access is a maximum of 4 weeks access for each 6 month period. Requests for additional time will require further justification.

### **Applicants to *Ultra* please note:**

*Ultra* offers access across three separate laser systems (see brochure for further information).

- Each laser system has both complementary (unique) and common capabilities. It is **strongly recommended**, especially for new applicants, that you contact an *Ultra* staff member to discuss your specific needs.



# Types of Access

- Direct Access (2 sides A4 - Peer review - 4 weeks)
- Programme Access (6 sides A4 – Peer review – 5 years)
- Proof-of-concept (Rapid Access) (Request to Facility Group Leader)
- Commercial or Industry Access (Discussion with Business Manager then contract)
- EU Access through Laser-Labs Europe – similar to Direct Access

# STFC Online Proposals Site



Science & Technology Facilities Council  
Central Laser Facility

High Power  
Lasers

Currently closed

Artemis

Currently closed

Octopus/Ultra  
Direct &  
Ongoing  
Programme  
Access

Currently closed

Octopus/Ultra  
New  
Programme  
Submission

Currently closed



Science and  
Technology  
Facilities Council

# STFC Online Proposals Site

## Impacts of inhaled particles on the brain. How particles translocate across the brain-blood-barrier?

22130017



We make [summary information available](#) for proposals awarded beamtime. For this type of proposal, we will publish the title and abstract.

Title \*

Impacts of inhaled particles on the brain. How particles translocate across the brain-blood-barrier?

Abstract \*

The communication from the lung to the brain, which is the "lung-brain-axis", is a hypothesis that explains the association between air pollution and incident cognitive decline, but it is yet to be proven. Toxicity studies using combustion-derived particles or surrogates is critical to developing a more in-depth understanding of the air pollution's impacts on mental health. This study will demonstrate if focused ion beam scanning electron microscopy (FIB-SEM) can be used to explore if and how particles translocate across the blood-brain-barrier (BBB), testing a key component of the lung-brain-axis hypothesis. The results would provide justification for future proposals seeking to use these techniques to further explore the mechanisms by which particles impact the neurological system.

Principal Investigator \*

Chang Guo; Public Health England

# The Scientific Case

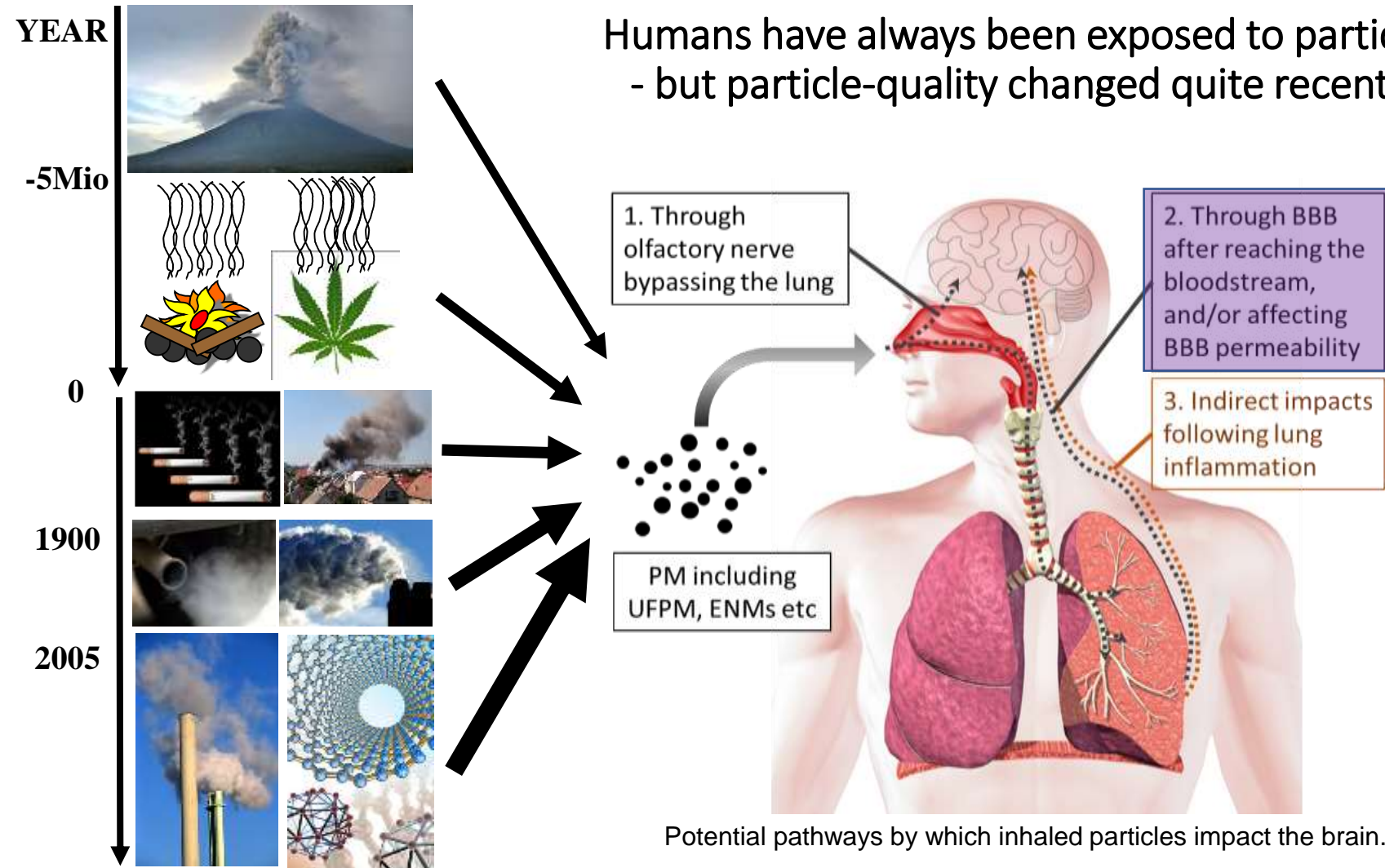
All science cases must adhere to the following format and use the headings marked in red:

- **Introduction and Aims:** Detail of the research idea / goals, aims and objectives. Define the major hypotheses to be tested.
- **Preliminary Data:** Include data observed or collected directly from research and/or development activities.
- **Justification for Facility and Equipment Requested:** Explain why you need access to the specific Facility – why can this not be done outside the specific Facility requested?
- **Measurable Expected Outcomes:** Describe the impact of the proposed work (international / national / academic / industrial / etc.)
- **Experimental Design & Methodology:** Provide a detailed experimental methodology and work plan in tabular or Gantt chart form.





Humans have always been exposed to particles  
- but particle-quality changed quite recently





## Impacts of inhaled particles on the brain

### - How particles translocate across the brain-blood-barrier?

#### Introduction and Aims

Worldwide, there are around 50 million people living with dementia and this number will triple over the next 30 years. Accumulating observations based on epidemiological studies have shown that exposure to air pollution, especially ambient particulate matter (PM), is an important environmental risk factor for neurodegenerative and neurological disorders, such as Dementia [1]. The highest concentrations of air pollution is prevalent in low and middle-income countries (LMICs), and around 60% of people with dementia in the world live in LMICs. Inhalation of unwanted air pollution is a primary source of environmental exposure and therefore impacts on public health. There has been a growing body of literature highlighting the impacts of traffic-generated air pollution on the central nervous system (CNS) including neuropathological outcomes in humans [2], which may be mediated by the inhalation of the particles. Current lack of understanding about the mechanisms by which air pollution impacts neurological health limits our ability to determine which components of air pollution lead to these effects and therefore to design effective policy.

Exposures to carbon- or metal-based nanoparticles (NPs) have been shown to induce different pulmonary diseases. The impact of inhaled particles beyond the lungs is indeed a pressing concern gaining recognition given the increasing acknowledgement of the systemic consequences of environmental toxicants. *In vivo* studies on rodents exposed to different types of nanomaterial-based particles confirmed that inhaled particles could impact the brain, either directly or indirectly. The inhaled particles can reach the brain through the olfactory nerve; or can potentially enter the brain across the blood-brain barrier (BBB) via systemic route.

The communication from the lung to the brain, which is the "lung-brain-axis", is a hypothesis that explains the association between air pollution and incident cognitive decline, but it is yet to be proven. Toxicity studies using combustion-derived particles or surrogates is critical to developing a more in-depth understanding of the air pollution's impacts on mental health.

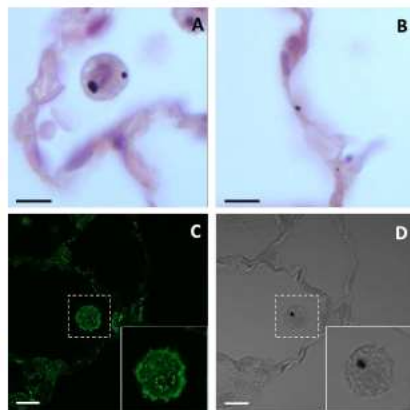
This study will demonstrate if focused ion beam scanning electron microscopy (FIB-SEM) can be used to explore if and how particles translocate across the blood-brain-barrier (BBB), testing a key component of the lung-brain-axis hypothesis. The results would provide justification for future proposals seeking to use these techniques to further explore the mechanisms by which particles impact the neurological system.

#### Preliminary Data

At the Public Health England (PHE) *in vivo* and *in vitro* inhalation studies have been undertaken to investigate the biokinetics and pulmonary toxicity of a range of aerosolized nanomaterials including Iridium NPs, AgNPs, CeO<sub>2</sub>NPs, iron oxide NPs, carbon nanotubes etc [3]. Uptake and retrograde axonal transport of (insoluble) particles via the olfactory nerve has been demonstrated in rodents for a number of engineered nanomaterials such as manganese oxide, titanium dioxide, iron oxide and silver. On the other hand, inhaled particulate aerosols would reach the alveolar epithelium lung with some captured by the macrophages as observed under a microscope (Figure 1, unpublished yet). Some of these deposited particles would be able to cross the alveolar blood barriers of the lungs first and enter into blood vessels directly or via lymphatic drainage.

#### Justification for Facility and Equipment Requested

The FIB-SEM at the Central Laser Facility (CLF) provides high-resolution (10-20 nm), material-sensitive ultrastructural imaging of 3D cellular volumes, which bestows a unique ability to aid the accurate and precise study of architectures of particle-cell interactions. The application of FIB-SEM within this proposal, would allow direct observation of the translocation of electron-dense combustion-derived particles or surrogates through the blood-brain-barrier (BBB). The size of the primary particles (either pure elemental carbon, or elemental carbon coated with various organics with different



**Figure 1. (A-B)** Pulmonary distribution of inhaled carbon-based nanoparticle aerosols in the rat lungs, as observed in the H&E staining of rat lung sections by light microscopy. **(C-D)** Confocal imaging of immunofluorescence staining of osteopontin (expressed in cytoplasm, in green) and deposited particles in rat lung tissues. Rats were exposed to carbon-based nanoparticle aerosols through nose-only inhalation pathway at  $1.71 \pm 0.23 \text{ mg/m}^3$  for 6 hours/day for 5 days/week for 4 weeks. Scale bars, 10  $\mu\text{m}$ .

oxidation states) is 70nm diameter range and would potentially be in aggregated form, as shown in Figure 1. The pollutants bear no fluorescent labels, however the cellular environment will be labelled and imaged with confocal microscopy. Therefore, correlating FIB-SEM with Confocal microscopy allows specific imaging and 3-D ultrastructural reconstructions of the regions of interest, herein tight junctions.

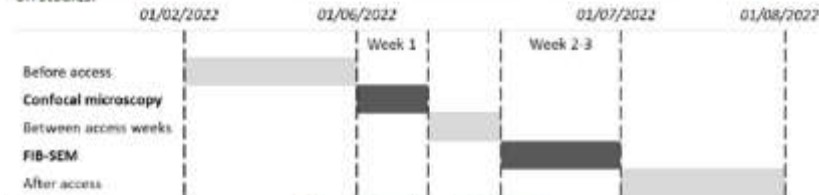
#### Measurable Expected Outcomes

Translocation of particles through the BBB is a key "lung-brain-axis" pathway through which particles could potentially impact the brain directly after they reach the blood circulation following inhalation. Measurable expected outcomes include imaging the samples in FIB-SEM to get molecular and ultrastructural details on the interactions between particles and cells in terms of paracellular- and/or transcellular-migrating and disruption of junction morphology.

Results of the imaging from the FIB-SEM would be linked to the biological toxicity effects and the bioactivity of tested particles, providing insight on neurological endpoints likely to be affected by exposure to air pollutants. The insights provided by this work could provide support for the "lung-brain-axis" hypothesis, demonstrating techniques that can be used to further investigate this pathway and beginning to build the scientific understanding of mechanisms that cause neurological impacts. This study will potentially contribute to building an evidence base to inform targeted regulations that can deliver improvements not just in air quality but also public health. While just a scoping study, this has the potential to lead to internationally important outputs providing direction for future research into air pollution related to neurodegenerative disease.

#### Experimental Design & Methodology

The proposed work is part of a project initially awarded through the innovative Collaboration Building Workshop organised by the STFC Air Quality Network (SAQN). This is a scoping study to trial a new application of an STFC facility. As such, if successful this would provide preliminary data to secure future funding for follow-on studies.



**Figure 2. Time flow in Gantt chart.**

**Before Access (12-16 weeks):** Identify the biological toxicity effects of tested particles in the BBB and monitor membrane permeability and the barrier integrity comparing different exposure conditions (exposure dose, exposure duration etc), so as to identify the suitable conditions for further analysis.

**Access:** Imaging for direct observation of the particles in the BBB (STFC, 1+2 weeks).

• **Week 1:** Perform fluorescence experiments to assess the interaction of the particle agglomerates with tight junctions. Here confocal microscopy at the CLF will be applied to image the tight junctions and to locate the particle agglomerates in cellular compartments that are necessary to determine further observations under the FIB-SEM.

Note: The images in Figure 1 show a type of carbon-based particle agglomerates with similar size as the tested particles in the lung tissues under light microscope and Confocal imaging, indicating the detection feasibility of the tested particles at low magnification for screening before applying FIB-SEM.

• **Between access weeks (1-2 weeks):** prepare samples for FIB-SEM.

• **Week 2-3:** Apply FIB-SEM for further observation of the particles in the BBB on selected conditions based on the assessments before, focus on the tight junctions of BBB (marked by fluorescently labelled junction adhesion protein in confocal experiments), and intracellular trafficking-involved compartments (e.g. lysosomes, tracked with LysoTracker in confocal experiments).

#### Selected References

1. Peters, R., et al., *Air Pollution and Dementia: A Systematic Review*. *J Alzheimers Dis*, 2019. 70(s1): p. S145-S163.
2. Sunyer, J., et al., *Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study*. *PLoS Med*, 2015. 12(3): p. e1001792.
3. Guo, C., et al., *Pulmonary toxicity of inhaled nano-sized cerium oxide aerosols in Sprague-Dawley rats*. *Nanotoxicology*, 2019. 13(6): p. 733-750.

# Facility Access Panel Review

- 10 – 12 Academics invited to sit on a review panel
- Mixed expertise
- Approx. 3 times over subscribed
- Applications tensioned on scientific merit
- Award time and feedback comments