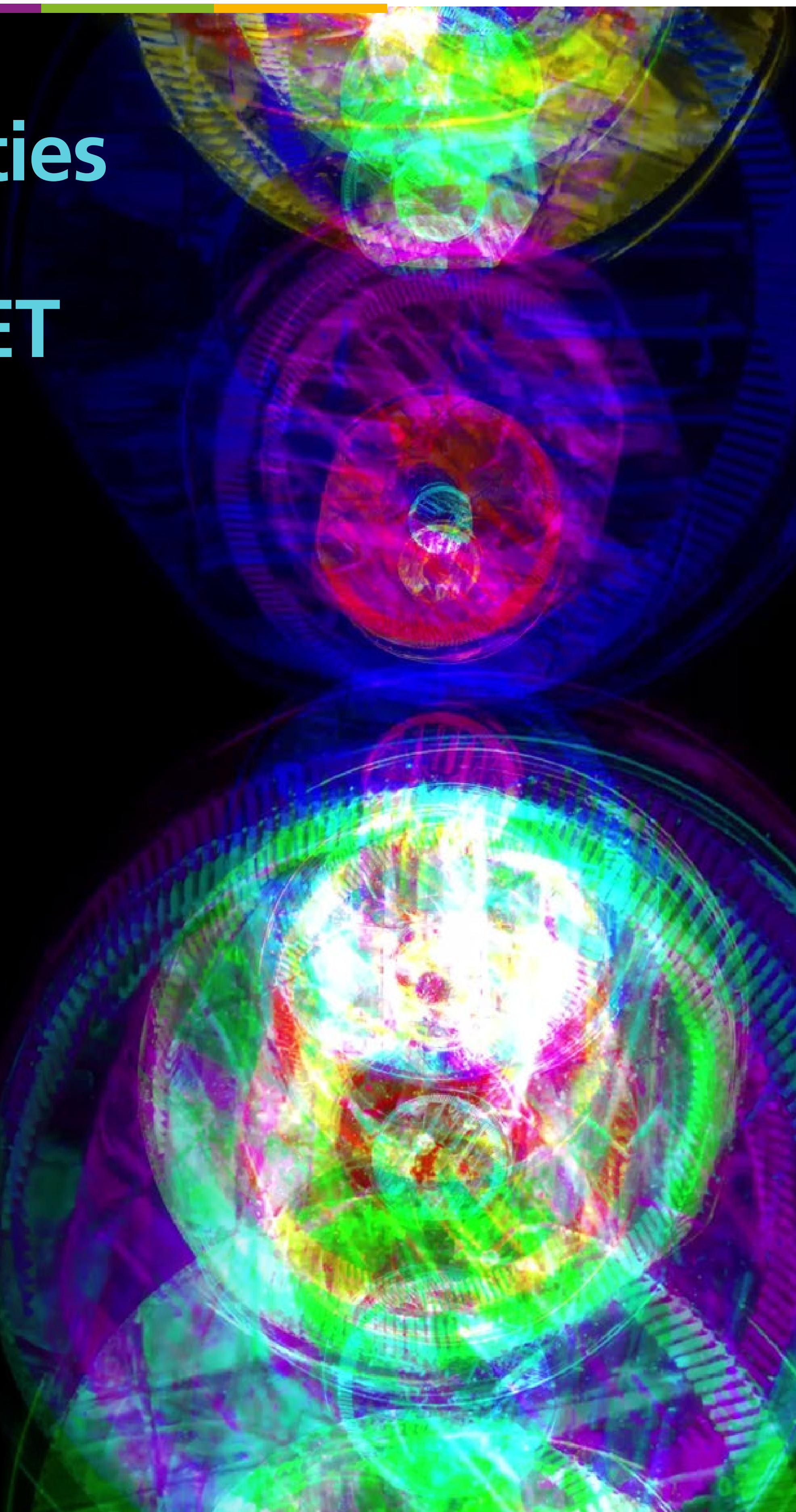
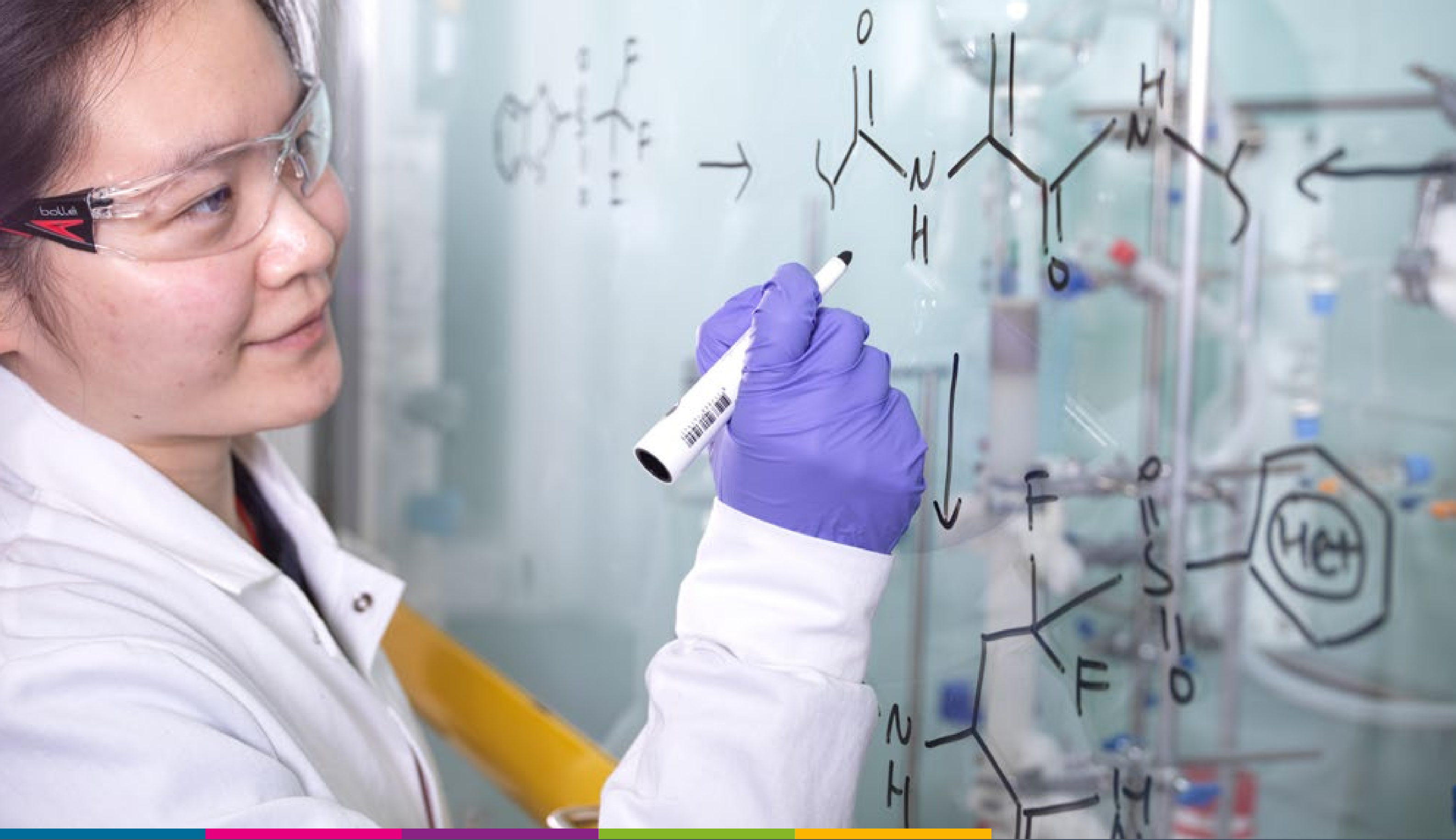
Report from the UK PET Innovation Network workshop on 6 September 2022

The Rosalind Franklin Institute

Opportunities for a National PET Innovation Centre





Executive summary

Positron Emission Tomography (PET) is a powerful medical technique for imaging the human body in health and disease. Yet despite its growing use as a diagnostic tool in the clinic, PET is still underused in basic research.

PET radiotracers can illuminate the biochemistry and thereby the mechanism of disease, and guide the discovery and development of new therapeutic drugs. However, PET researchers in the UK are hampered by a lack of dedicated infrastructure to produce and exploit the novel radiotracers that are central to this technology.

In September 2022, the community-led UK PET Innovation Network (https://www.petnetwork.org.uk/) organized a one-day symposium which included discussion on a proposal for a nationally accessible pre-clinical PET Innovation Centre at the Franklin. This centre would produce a broad palette of PET radioisotopes so that researchers could develop and apply novel radiotracers to study fundamental biological processes. The facility could play a critical role in helping the UK to realize its Life Sciences Vision, and strengthen the UK's position as a global science and technology superpower.

During the workshop, an international panel of speakers discussed their experiences of running world-class PET research centres, and considered how a new PET Innovation Centre might serve as a hub integrated with the UK PET Innovation Network for research collaborations between academia and industry.

The centre could be hosted by the Rosalind Franklin Institute, an institute dedicated to creating novel technologies to understand the biochemical mechanisms of life. PET would join a suite of techniques at the Franklin that enable researchers to understand diseases in more depth than ever before, through a form of 'atomic pathology'.

Research at the centre could identify new biomarkers of disease, for example, which would help clinicians to diagnose patients earlier and with more accuracy. It could help to create and validate new PET radiotracers that monitor the effectiveness of experimental drugs during clinical trials, or assess how patients respond to existing treatments. Working with the UK's proposed new total-body PET centres, announced in July 2022 by UKRI-MRC, a national PET Innovation Centre coupled with strong links to networks, such as the UK PET Innovation Network, to translate such discoveries into the clinic. It would also play a pivotal role in training the next generation of PET researchers.

This report offers a starting point for further community discussions about the opportunities of a PET Innovation Centre, and invites potential collaborators to offer further input by contacting

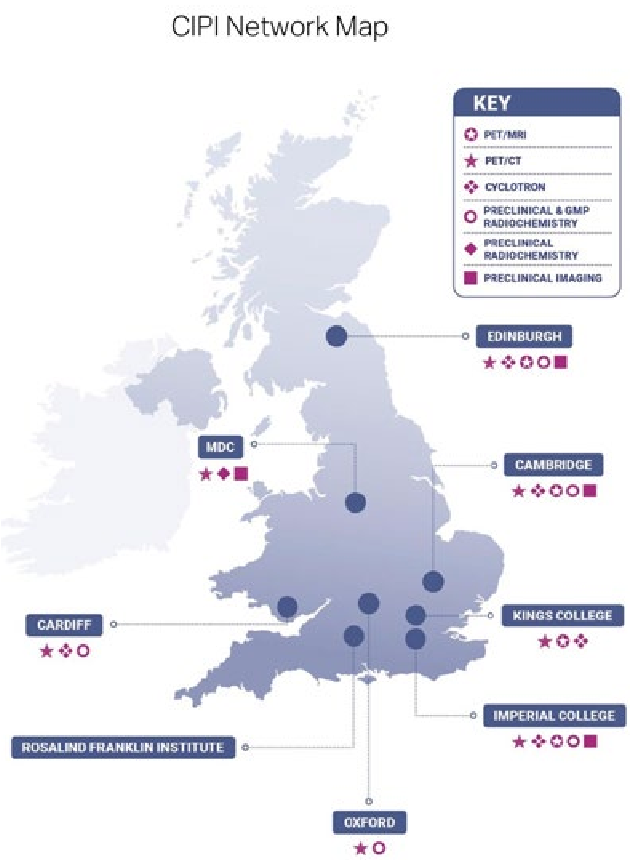
Professor Ben Davis at info@rfi.ac.uk.

Introduction

Positron emission tomography (PET) is an incredibly sensitive technique that can track and quantify biochemical processes inside a patient's body, in real time. It uses compounds labelled with radioisotopes to produce radiotracers to visualise biological molecules, cells, living tissue and organs, and illuminate physiological changes such as blood flow or the growth of a tumor.

PET imaging has seen accelerating clinical use since the 1990s, in the UK and around the world. For example it plays a vital role in cancer diagnosis, and in assessing the progression and mechanism of neurodegenerative disorders such as Alzheimer's disease. Recent years have seen the development of total-body PET scanners that are large enough to image an entire patient and have greatly enhanced sensitivity. In July 2022, UK Research and Innovation confirmed that it would invest in a new translational total-body PET centres.

The UK now has a historic opportunity to expand the use of PET — not only in the clinic, but also in research laboratories, where it can answer fundamental questions in biology. PET can reveal the underlying biochemical mechanisms of disease, for



The UK PET Innovation Network brings together researchers and facilities from across the country. (Credit = UK PET Innovation Network).

example, guiding drug discovery programmes and helping to assess the effectiveness of experimental medicines. This research will ultimately improve how people are diagnosed and treated for a range of diseases in the decades to come. However, PET is currently underexploited in basic research, in part because researchers often have limited access to the infrastructure and radiotracers they need.

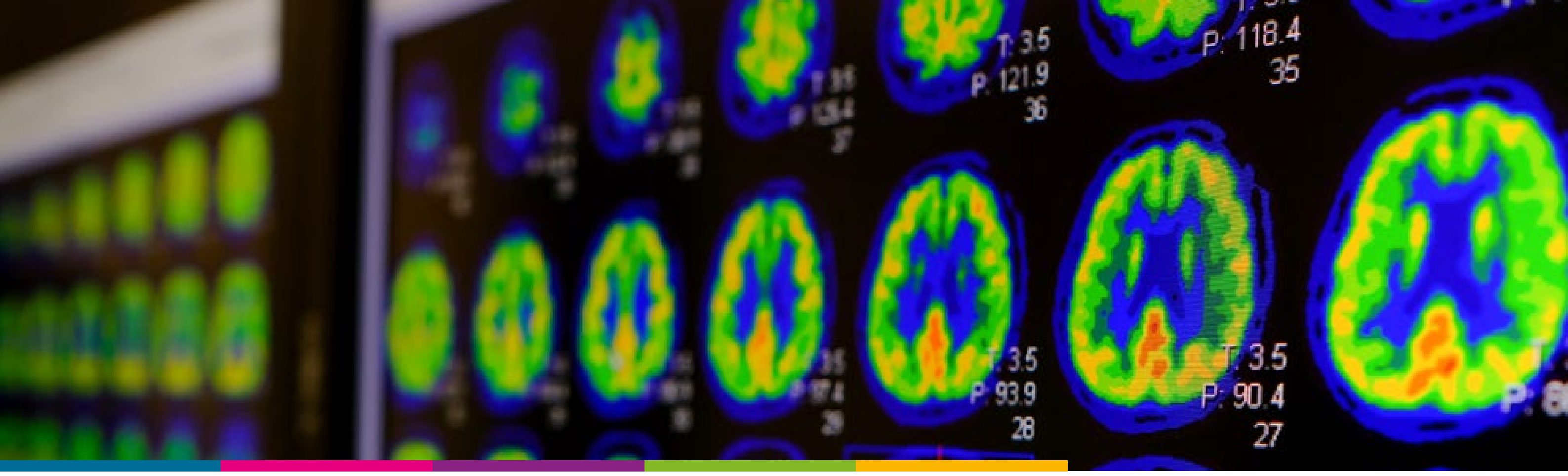
The UK PET Innovation Network (https://www.petnetwork.org.uk/) is a community-led initiative that launched in 2020 to help overcome the bottlenecks that are holding back PET research in the UK. The network aims to enhance innovation and collaboration in PET; to increase the technique's impact in biomedical research and clinical applications; and to accelerate the translation of new PET technologies. The network initially included seven leading academic PET centres of excellence, along with the Rosalind Franklin Institute, the Medicines Discovery Catapult, AstraZeneca, GE Healthcare and GSK. Its future aim is to broaden this membership

On 6 September 2022, the UK PET Innovation Network hosted a one-day symposium at the Harwell Science and Innovation Campus, home of the Franklin. In addition to presentations from key clinical PET networks and leading UK and international researchers, the symposium included a townhall discussion about a proposal to create a national PET Innovation Centre for the UK, which would act as a flagship research centre and a nexus for national and international collaboration, which would have strong links to networks, such as the UK PET Innovation Network, to facilitate these collaborations.

The workshop also included a panel discussion on 'International Models for Innovation Centres in Radioscience', featuring leading researchers from the UK, US and Finland. Several of the speakers have direct experience of setting up world-class PET research facilities, and their insights helped to address questions such as:

- What scientific questions should a national PET Innovation Centre address?
- What would a national PET Innovation Centre look like?
- How would researchers access the centre?

This report summarises key points from all these discussions, and offers a first glimpse of how a nationally accessible PET Innovation Centre could



help to transform basic PET research, training, drug discovery, and clinical practice.

Watching biochemistry in action

PET relies on molecules called radiotracers that carry positron emitting radioisotopes. These are designed to accumulate in specific parts of the body, or in particular cell types. When PET radioisotopes decay, they emit positrons — the antimatter counterparts of electrons. These positrons quickly combine with ordinary matter to release gamma rays. PET scanners detect these gamma rays to build up a 3D image that shows the distribution of the radiotracer inside parts of a patient's body.

The most common radiotracer is fluorodeoxyglucose (18F-FDG), an analogue of glucose. It accumulates wherever there is a high uptake of glucose in the body, including tumor cells and brain cells, making it extremely useful in cancer diagnosis and neuroscience.

Radiochemists have a range of PET radioisotopes at their disposal, most of which are generated by particle colliders called cyclotrons, and these radioisotopes have been incorporated into hundreds of different radiotracer molecules. Each radiotracer has unique properties that can be harnessed for specific imaging tasks.

PET isotopes don't last long, though. Fluorine-18 (18F) has a half-life of 110 minutes, which means that the amount of radioactivity released by an 18F radiotracer halves every couple of hours. Other PET isotopes have half-lives that range from a few minutes to a few hours. These short timescales mean that the isotopes must be incorporated into the radiotracers using simple, quick and reliable radiochemical reactions — a key challenge for the radiochemists who develop new tracers.

Due to their brief lifespans, PET isotopes are usually created in dedicated facilities, often with a cyclotron for local generation of the radioisotopes inside hospitals, so that fresh radiotracers can be produced and injected into patients before losing too much of their radioactivity. These facilities also enable ground-breaking research, but they can be hampered by the need for the regular productions of established radiotracers like 18F-FDG for use in the clinic.

This poses a major impediment for basic PET radiochemistry research. The required PET radioisotopes and radiochemistry facilities are not always available for researchers when they need them; thereby reducing the development rate of novel radiotracers and radiosynthetic methods.

There is also a global shortage of radiopharmaceutical scientists, but the lack of research radiochemistry laboratory infrastructure in the UK means that there are insufficient opportunities for training. Moreover, small- and medium-sized enterprises (SMEs) that work in biotech or pharmaceutical development often do not have the in-house knowledge they need to use PET as a tool in their research.

To help tackle these problems, the Oxford Imaging Methods Epicentre (OxIME) aims to create a pre-clinical PET Innovation Centre that is nationally accessible. It would feature a cyclotron to generate PET radioisotopes for research; laboratories hosting 'hot cells' that are suitable for handling those radioisotopes; and an animal facility for in vivo imaging. It aims to be an innovation engine that would forge PET research collaborations across academia and industry, drawing in researchers eager to take advantage of its world-class facilities.

The Franklin could offer a suitable home for this centre as part of its next phase of investment and expansion. Its mission statement is to develop and exploit technologies that enable the 'imaging of life in five dimensions' — to study biomolecules in the context of space, time, and chemistry. The knowledge gained from mapping the complex chemical processes that underlie diseases will help to deliver tools that can diagnose diseases earlier and more accurately, and to develop the medicines and other interventions needed to tackle them.

PET is one of the leading enabling technologies in this quest. Radiotracers can closely mimic biological molecules, so they shed light on chemical mechanisms in the body without disrupting them. By studying the distribution of PET radiotracers within tissue, researchers can draw a direct link between activity at the molecular scale, the behaviour of cells and tissues, and the physiology of diseases in entire organs. In essence, it promises a kind of 'atomic pathology'.

Scientific opportunities

Each PET radiotracer is a precision tool that can answer a particular biological question, so developing new radiotracers is naturally a core part of PET research. A PET cyclotron dedicated to pre-clinical research could supply a broader palette of radioisotopes, and help to invent new radiotracer molecules to carry them to their intended destinations in cells and organs. At a nationally accessible PET Innovation Centre, radiochemists could then validate such radiotracers using other chemical and molecular biology techniques (including various forms of microscopy available at the Franklin) to confirm what their radiotracer reveals about the biology of a living system.

The Franklin's focus on structural biology also puts it in an ideal position to use PET for biomarker discovery. Biomarkers are red flags that signal the progress of a disease, and clinicians sometimes rely on just one or two biomarkers for their diagnoses. Identifying new biomarkers can therefore enable more watertight diagnoses in the clinic. For example, basic research using PET might identify a particular protein that is indicative of the early stages of a neurodegenerative disorder, making it a useful biomarker. PET can also probe how changes in that protein might influence the progression of the condition — how it misfolds or how it is circulated, for example. Understanding that mechanism gives drug developers important clues about how to design new medicines that can target these proteins.

There are now huge amounts of genomic data available to researchers, and increasing amounts of additional 'omic' data about other functional biological molecules. With the help of PET, this data could be tapped to illuminate the causal chain that links genes to the causes and symptoms of disease. In this way, a coherent approach could be used for nucleic acids, carbohydrates, lipids and other biomolecules involved in every aspect of biology.

With these strengths in basic research, a national PET facility could host collaborations with the biotech and pharmaceutical industries, where PET is currently rather underused. It could also help to simplify the procedures used to prepare PET radiotracers — by increasing the use of automation, for example — potentially lowering costs and facilitating more routine use of PET.

Beyond understanding the fundamental biology underlying disease processes, and identifying the cell types that treatments should target, PET can offer a way to monitor the action of experimental drugs during clinical trials, providing essential evidence about their effectiveness. In combination with other imaging techniques like computed tomography (CT), magnetic resonance imaging (MRI), and tissue mass spectrometry, this can build up a stronger evidence base for a drug before it moves forward into larger — and more expensive — clinical trials. This 'de-risking' approach could help to weed out drug candidates that are more likely to fail, before vast amounts of money are spent on trials. This is particularly relevant for biologic drugs such as antibodies or proteins. Biologic drugs have seen a rapid uptick in use over the past decade, but they can have more complex interactions with the body than small-molecule drugs, increasing the chances of biologic drug candidates failing during late-stage clinical trials.

Radiochemists can also design PET radiotracers that reveal how patients respond to clinically-approved treatments. For example, if a PET scan shows that a cancer drug is working well, clinicians can scale back the chemotherapy to minimise side effects; and if it isn't working, they can switch to an alternative treatment altogether, to avoid causing undue side effects.

Having developed an effective PET radiotracer for imaging specific biomolecules or cells, researchers could even swap the PET isotope for another isotope that delivers a different kind of radiation to kill those cells. In this way, basic research on an imaging agent can be translated into new forms of radiotherapy.

PET has traditionally focused on cancer and neurological disorders, but far less on infectious diseases or immunology. For example, rheumatoid arthritis is an autoimmune disease — X-ray is the standard technique used to see how it damages joints, and MRI can reveal some of the inflammation connected to the disease. But the pharmaceutical industry needs a tool, such as PET, to study how drug candidates affect the molecular biology of the immune system underlying these effects. A national PET centre could engage in long-term collaborations to develop the radiotracers needed to carry out these studies.

Learning from others

The meeting's panel discussion featured guest speakers from radioscience innovation centres in Finland and the United States, who offered advice about how they established and operate their facilities (see box, overleaf); and a research leader from the pharmaceutical industry, who outlined how industry collaborators could benefit from such a centre in the UK. The panelists were:

- Professor Ben Davis, the Rosalind Franklin Institute, Harwell, UK
- Professor Jason Lewis, Memorial Sloan Kettering Cancer Center, New York
- Dr Phil Murphy, the Janssen Pharmaceutical Companies of Johnson & Johnson, High Wycombe, UK
- Professor Olof Solin, University of Turku / Turku PET Centre, Finland
- Dr Amy Vavere, St. Jude Children's Research Hospital in Memphis, Tennessee

Following the panelists' presentations, the audience participated in a lively discussion about the potential of a national PET Innovation Centre, contributing many ideas about how it might operate, and the opportunities it would offer.

There was general agreement that the centre would ensure UK researchers have more reliable access to the radioisotopes they need. Although 18F and carbon-11 (11C) are more routinely produced in the UK for clinical use, some key PET isotopes such as zirconium-89 are often imported from abroad. A national PET Innovation Centre should offer a broad range of isotopes to help address that supply chain vulnerability.

Flexible design will be an important consideration for the new facility. Once a cyclotron and hot cells are in place, it is very difficult to move them around. So the facility has to be planned with enough space for future expansion as new PET technologies emerge, in order to capitalise on the latest advances in the field.

An initiative at King's College London could offer useful pointers about different access models for researchers. King's plans to open the Cyclotron and Radioscience Laboratory (CARL), a PET facility that will be open to external users, in July 2023. These users are likely to access the facility in four different ways. External researchers could simply come there to carry out specific research projects; the facility will also produce radioisotopes or radiotracers that can be shipped out to researchers; and it will organise training activities for external researchers. The main route, though, will likely be through formal collaborations with external researchers, supported through joint funding applications. CARL would therefore be complementary to a national PET Innovation Centre — but the experience gained at the King's facility could also guide how a larger national facility might work.

Young researchers would particularly benefit from collaborations with a national PET Innovation Centre. Radiochemistry is expensive, so early-career researchers could access the facilities they need to generate data, as a stepping stone to their first independent research grants. Meanwhile, industry researchers should be able to access the centre to solve specific problems around a particular drug or biochemical system; and to participate in long-term collaborations that focus on more fundamental questions of biology.

The centre should also be open to international collaborators, including students and post-doctoral researchers. Through this exchange of expertise, a national PET Innovation Centre could become a crucial node in a global network of PET research.

Planning for excellence

As a national facility, the centre will play a pivotal role in training. The field of PET is highly interdisciplinary, involving researchers across the scientific spectrum: chemistry, physics, and biology, all feeding into clinical practice. Few individual scientists working in PET currently have expertise in all these areas, but the next generation of PET scientists could be trained in a multi-disciplinary way from the outset, giving them the broad knowledge needed to advance the field.

The centre would focus on pre-clinical research — as such, it would not have a laboratory capable of preparing radiotracers according to the good manufacturing practice (GMP) standards necessary for their use in human subjects. But it will be possible for the centre to evaluate new tracers for their suitability for clinical use, especially with the help of clinical collaborators. The needs of these collaborators will help to define the research agenda of the centre, so it must forge strong links with key clinical stakeholders. Innovations at the centre could eventually be trialed at the UK's new total-body PET centres, illustrating how a pre-clinical research facility can support broader clinical translation.

The MRC Laboratory of Molecular Biology (LMB) offers an instructive model in this regard. It does not work directly with patients, but it has had an enormous impact on medical treatments — indeed, it has been a global beacon for molecular biology research that has attracted the best researchers from around the world.

That makes it vital for the PET Innovation Centre to operate in a way that makes it as easy as possible for researchers to tap its resources. It is unlikely to function as a user facility, such as Diamond Light Source, where external researchers are allocated limited time slots to use the facilities. Instead, it would aim to work with

Turku PET Centre, Finland

The Turku PET Centre is a Finnish national research institute based at the campus of the University of Turku, and Turku University Hospital. It mainly focuses on producing isotopes for biomedical research, but also provides diagnostic isotopes for clinical use. The centre was established in the 1970s, became a national facility in 1996, and is routinely involved in PET collaborations.

The centre has a staff of about 200 people, who collaborate with researchers visiting the centre to work on specific research projects. The centre's infrastructure includes eight PET scanners, three cyclotrons and two gallium-68 (68Ga) generators; there are radiochemistry labs for research and teaching, and another that produces radiotracers to good manufacturing practice (GMP) standards that can be used in experimental studies on human subjects. In all, they have 26 hot cells, and more than 40 radiotracers are in routine use at the centre.

Molecular Imaging Core at St. Jude Children's Research Hospital, Memphis, Tennessee

The Molecular Imaging Core was created about five years ago and uses PET to support clinical trials and pre-clinical research. It has a cyclotron (along with two in-house cyclotron engineers), a radiochemistry laboratory with eight hot cells, and a lab that ensures products meet GMP standards.

The Core works as a collaborative hub for researchers across the hospital, and it has been involved in developing four radiotracers to investigational new drug status. It also raises awareness among clinical investigators at St. Jude about the opportunities of PET, and works with them to develop and supply the tracers they need for their studies.

Radiochemistry & Molecular Imaging Probes Core at Memorial Sloan Kettering Cancer Center, New York

The Radiochemistry & Molecular Imaging Probes Core works with clinical investigators at the center to develop and translate radiopharmaceuticals for clinical use against cancer. It has a cyclotron that makes a wide variety of isotopes, along with four 68Ga generators, to produce imaging tracers and therapeutic agents for routine clinical use, as well as basic research. The Core works on a cost recovery model, effectively 'selling' its services to internal users.

external researchers in collaborations that could span from 3 months to 10 years.

Engagement with potential collaborators will obviously be a core element of the centre's work, and must also guide its evolution. So the Franklin is now calling for further community input to help shape the development of a national PET Innovation Centre. To get involved, please contact Professor Ben Davis at info@rfi.ac.uk.

Conclusions and next steps:

The Franklin believes that the PET centre has sufficient community support to merit inclusion of the centre in its phase two planning.

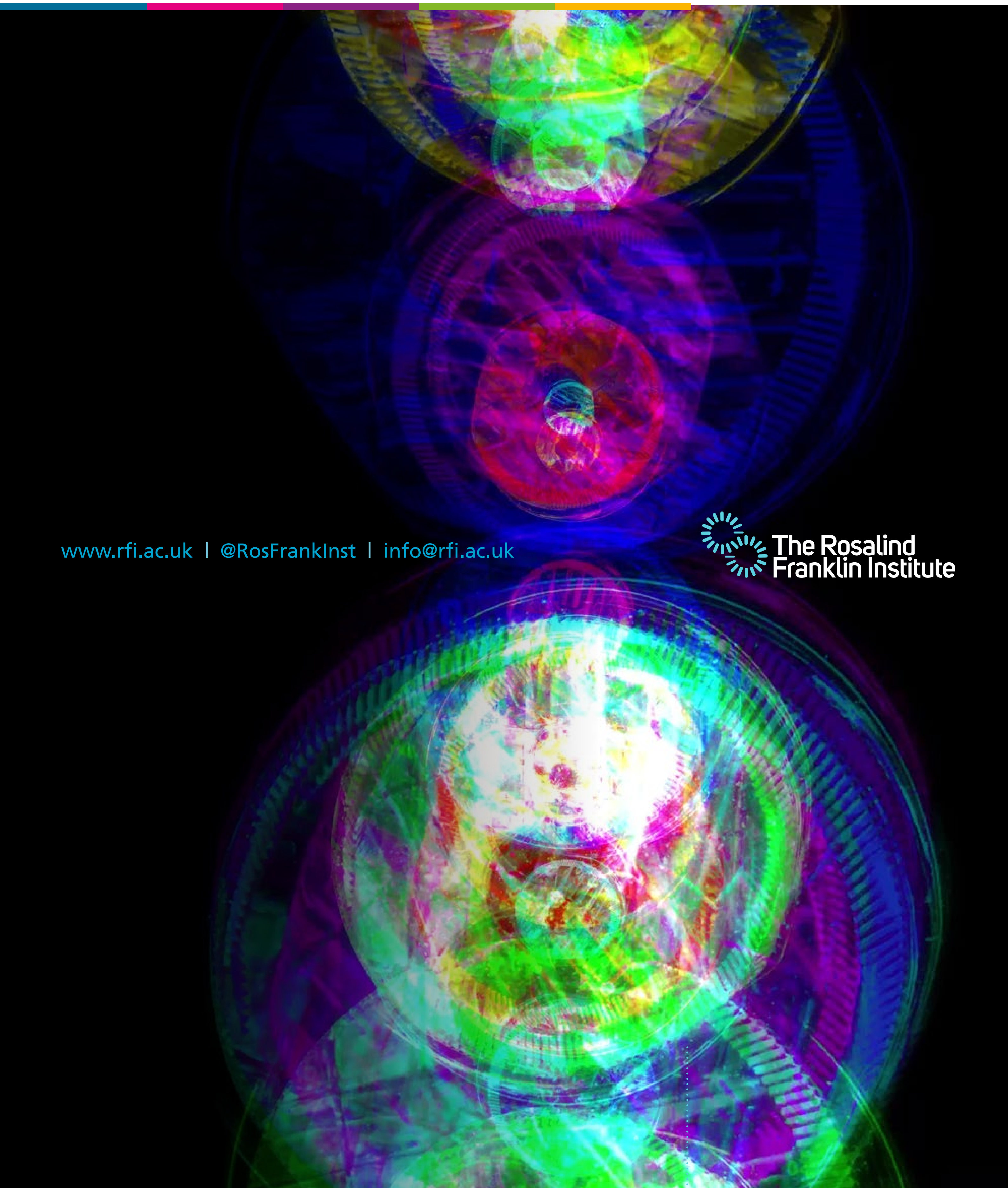
Consultation will continue with the UK PET Innovation Network on specifications, community collaboration model and plans for training and development of the community around this important technique.

We propose to work with funders across the UK landscape to ensure that the centre accesses new research communities which might make use of the facility, and to consult with industry to ensure SME and larger pharma can collaborate successfully for the benefit of the UK.

Appendix

Thank you to the delegates at the UK PET Innovation Network workshop on 6 September 2022 for their input into discussions, we hope to work with many of you going forward.

This report was prepared for the Rosalind Franklin Institute by science writer Mark Peplow.



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