Imperial College London

MULTI-FACULTY CENTRE OF EXCELLENCE

ANNUAL REPORTING TEMPLATE

Introduction

Imperial College Multi-Faculty Centres exist to galvanise a critical mass of permanent academic staff and funding, through multiple research groups, around a multidisciplinary theme. They provide an advantage to Imperial by creating a structure that transcends Faculty boundaries as required for the progression of the scientific endeavour. Their existence brings identifiable benefits regarding, for example, growth, breadth, and internal and external visibility. Multi-Faculty research Centres are advantaged by Imperial in terms of institutional recognition and branding. They will have a formal and visible presence in the web architecture of the College providing prominence and connectivity to College senior management. They also have the potential to access strategic funding at the discretion of the Vice-Provost Research.

Purpose

The purpose of this report is to:

a) Provide the Vice-Provost's Advisory Group for Research with a progress report to assure that College approved Multi-Faculty Centres are meeting their planned objectives or provide explanation where there is variance;
b) Allow the Vice-Provost's Advisory Group for Research to review and where appropriate refresh the College's portfolio of Multi-Faculty research Centres and Networks;
c) Allow the Centre to highlight successes/achievements so that these may be further highlighted to stakeholders as appropriate;
d) Allow the Centre to highlight current or predicted barriers to progress so as to initiate further discussion as appropriate.

Review of Report

The report will be reviewed initially by the relevant Vice-Dean (Research) and subsequently by the Vice-Provost's Advisory Group for Research.

Submission of Report

Please submit your completed report and an updated membership list to researchoffice.fundingstrategy@imperial.ac.uk by 1st November 2018.

Section 1: Multi-Faculty Centre Summary – please use Section 3 to provide explanation of any changes from the original information provided.	
Name of Director	**Kenneth Long**
Name(s) of co-Director(s) (if applicable)	
Name of Deputy Director(s) (if applicable)	
Name of Host Department	Physics
Title of Centre	Centre for the Clinical Application of Particles
Web address of Centre	https://www.imperial.ac.uk/clinical-application-of-particles/

Social media accounts	None
Start Date of Centre (dd/mm/yyyy)	01/10/2017
Number of FTE associated with the Centre	Membership: 61 FTE: 8.8 (FTE count from notional weighting of time spent on Centre activities)
List of current Departments involved in the Centre	Imperial: Physics, Surgery and Cancer, Imperial Academic Health Science Centre Other: Institute for Cancer Research, John Adams Institute, Oxford Institute of Radiation Oncology
List of current Faculties involved in the Centre	Natural Sciences, Medicine

Section 2a: Funding – P codes

Please provide a list of P codes representing the funding associated with the Centre since its inception (which may have been before College approval). This will be used by the Research Office to summarise expenditure and the current budget available over the next three years.

P code	*Sponsor*	*Start*	*End*	*Value (1) £k*	*Scaled to Apr18 £k*	*Attribution to CCAP*	*Value (2) £k*
P54038	STFC	01Oct14	30Sep19	297.61	297.61	0.1	14.88
P63353	STFC	01Oct16	31Mar20	991.42	743.57	0.1	74.36
P28063	EPSRC	21May13	20May19	1,017.01	678.01	1.0	678.01
P66857	STFC	01Jan17	30Sep19	84.72	84,715	0.1	8.47
P63914	STFC	01Apr17	31Mar21	1,555.57	1,555.57	0.1	155.56
P48107	STFC	01May13	30Apr23	390.06	78.01	0.1	3.90
P56866	STFC	01Jan15	31Dec19	191.30	114.78	0.1	5.74
P55678	STFC	01Oct15	30Sep19	147.55	73.78	0.1	7.38
PSF883	STFC	01Aug18	31Mar19	52.10	52,104	1.0	52.10
P65375	STFC	01Jan18	31Dec20	39.88	39,880	1.0	39.88
Will be G account	STFC	01Oct18	30Sep22	87.56	87,563	0.1	8.76
Total							***1049.03***

The P codes representing funding associated with the Centre are listed above. The accounts listed in the first block (i.e. above the line) were in existence when the Centre was formed. The total value of each award (Value (1)) has been scaled to 01Apr17, the start of the financial year. The accounts in the second block (below the line) have been won since the Centre was formed. Additional support for the Centre's programme is being provided by the Imperial CRUK centre, and by the Imperial/NIHR BRC.

For each award an 'Attribution' has been estimated to reflect the fraction of the full award that is directly in support of the Centre's activities.

Section 2b: Funding – N codes

Please provide details of any other research income not on P codes associated with the Centre since its inception (which may have been before College approval). This will be used by the Research Office to summarise expenditure and the current budget available over the next three years.

Imperial College London

Source of Funding	Total Budget Awarded	Award Period
None.		

Section 2c: Funding – Core costs

Please provide a summary of any core costs required for the function of the Centre (e.g. admin, or director time) and how these are currently met.

There are two core posts associated with the Centre; the Director and the Manager. The Director is a permanent member of the academic staff in the Physics Department and is supported through STFC (P54038, P55678) and the Department. Agreement has been reached for the cost of the Centre Manager to be born jointly by the Department of Physics and the Department of Surgery and Cancer. Details of this arrangement are still being worked out.

Section 3: Scope and Objectives

Please provide a summary of any changes to the purpose and scope of the Centre being sure to provide clarity where there may be perceived overlap between this Centre and other College entities. For the latest list of Multi-Faculty Centres and Networks see: https://www.imperial.ac.uk/multidisciplinary-research/

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The mission of the Centre for the Clinical Application of Particles (CCAP) remains to:

Develop the technologies, systems, techniques and capabilities necessary to deliver a paradigm shift in the clinical exploitation of particles.

The Centre's Management Board is developing a Business Plan articulating the vision that underpins the Centre's scientific, technology-development, and technology-transfer ambitions; lays out the programmes and investment required to deliver these ambitions; and sets out the alignment of the Centre's multi-disciplinary programme with the expectations of the various funding agencies. The strategic themes identified in the Centre's Business Plan are:

- The development of novel, compact, laser-driven accelerator systems for clinical application;
- The development of novel, real-time diagnostic, imaging, data-processing, and machine-learning techniques for clinical application;
- The delivery of a broad programme of measurement of the radiobiological effect of particle beams;
- The staged implementation of a dedicated laser-driven accelerator dedicated to the systematic study of the micro-biophysical processes induced by photon, electron, proton and light-ion beams; and
- The establishment of the network of national and international collaborations necessary for the CCAP to initiate and then to sustain its radiobiological and technology-development programmes.

The Centre's laser-driven radiobiology facility has the potential to be a world-leading facility in its own right and will also prove the Centre's novel accelerator, detector and data-processing technologies.

There are three multi-disciplinary networks and two multi-disciplinary centres at Imperial working in fields related to the activities of the CCAP. The goals of each of these networks and centres are complementary to, but do not overlap with, those of the CCAP. Links exist between the CCAP and the Cancer Technology Network; information is shared and each entity advertises the other's events. The expertise that resides within the Innovative Imaging Network (IIN) is likely to be of benefit to the radiotherapy (RT) image-processing activities of the CCAP. An application for an STFC CASE Studentship has been made (Charing Cross Hospital (CXH), Imperial Physics, and Maxeler Technologies). Should this proposal be granted, the informal contacts that exist between the CCAP and the IIN will be strengthened. In part prompted by the preparation of this annual report, contact has been made with the remaining network (the Industrial Biotechnology Hub) and the two centres (the Integrative Systems Biology and Bioinformatics and Mathematics of Precision Healthcare Centres) with a view to exploring areas of mutual interest.

Section 4: Overview of Centre activity undertaken to date

Please describe the activities undertaken since the Centre's approval - this should include:

- Management Board meetings held;
- External Advisory Board meetings held (where appropriate);
- A summary of any outreach or public engagement activity conducted by the Centre including number of people engaged and any funding applied for/received (link to P/N code listed in section 2);
- A summary of any postgraduate training activity conducted by the Centre including number of students undergoing training and any funding applied for/received (link to P/N code listed in section 2);
- A summary of any industrial engagement activity conducted by the Centre including any funding applied for/received (link to P/N code listed in section 2).

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Plenary meetings

In addition to regular topic-specific meetings between staff associated with the Centre, the Centre brings together members from across it's institutes at larger half-day plenary meetings at which their research is discussed. Two such meetings have taken place; 28th November 2017 and 18th July 2018. The next meeting will take place on 6th November 2018.

The first of these meetings was held shortly after the Centre was formed and focused on how it could make an impact in the short, medium, and long terms. Members introduced themselves and their research, and lively conversation ensued. One outcome of this meeting was a multi-disciplinary proposal on ultra-fast prompt-photon imaging for proton beam therapy that was submitted to the Imperial Excellence Fund for Frontier Research. In addition, it was agreed that the Centre should develop an application for an Innovative Training Network (ITN) and members were identified to take the lead in preparing the proposal. Potential collaborations with laboratory or industrial partners were presented and discussed; examples include partnership with ISIS Division at the STFC Rutherford Laboratory (RAL) to exploit the synergies with the ISIS II upgrade; collaboration with the STFC Daresbury Laboratory (DL); opportunities to work with MedAustron and the Medical University of Vienna; and collaborative opportunities with the CNAO-based FragmentatiOn Of Target (FOOT) experiment.

At the second meeting (18th July 2018) members presented updates on the research carried out in pursuit of the Centre's goals. Largest amongst these was the initial steps toward the design of a radiobiology facility using a laser-based proton and ion source and novel beam-capture and transport. Summaries were also given of regular simulation and experiment meetings, highlighting their use to all students and postdocs within the Centre. Finally, a report was given by an Imperial College student (H. T. Lau) who had begun to contribute to the commissioning of the carbon-ion beam-line at MedAustron.

Management Board meetings

Two Management Board meetings have been held in this reporting period; 5th December 2017 and 18th July 2018. These meetings are held at six-month intervals. The next meeting will be held on 6th November 2018.

The first meeting of the Management Board (5th December 2017) took stock of the research of the collaborating institutes and discussed the path toward making an impact through research proposals. The Management Board initiated the preparation of a 'Business Plan', in which the goals, scientific programme, and project plans would be set out. The Board members were invited to a meeting at MedAustron to visit the facility and to discuss opportunities for collaboration. Finally, a seminar series and a clinician-led meeting were initiated, the latter to be arranged between clinicians at CXH and the Institute of Cancer Research (ICR) to highlight the patient pathway and current technology.

The second Management Board meeting (18th July 2018) brought the need for a collaboration agreement between institutes to the attention of the Board. The concept for the Business Plan was refined and lead authors were identified for the sections dealing with each of the Centre's three main research themes. The Management Board set a deadline of Autumn 2018 for a first draft of the Business Plan. The Board agreed that the International Advisory Board should be instituted once the Business Plan was in place and that it should be asked to review and comment on the Plan at its first meeting.

In addition to these discussions, research synergies between the ICR and the CXH were identified in the area of high-dose-rate and electron-micro-beam radiotherapy. These synergies are being pursued within the CCAP by the key proponents.

Interdisciplinary meetings:

A half-day meeting took place at the CXH on the 5th February 2018 to show the state of the art in radiotherapy. The meeting, which was organised jointly by clinicians from the CXH and the ICR, was attended by approximately 20 CCAP members. The goal of the meeting was to allow the Centre's physical scientists to see the equipment in the clinic, to better-understand the patient journey, and to have some sight of the issues faced by clinicians and patients. Each step in the patient journey was explained and the challenges associated with it were discussed.

Monthly simulation and experiment meetings have been organised to allow students and post-docs to discuss computing issues and to learn about the resources available in the groups affiliated to the Centre. An update on these meetings is given at each plenary meeting.

Training activities

The Centre has one PhD student, recruited through the HEP Group, placed with an industrial/laboratory partner, MedAustron. MedAustron provides accommodation for the student during his secondment at the laboratory. The student is contributing to the carbon-ion beam line commissioning, and will shortly transition to the development and exploitation of instrumentation for radiobiological studies.

An STFC CASE Studentship proposal has been submitted between the CXH, Imperial Physics, and Maxeler Technologies. This programme is designed to develop fast, adaptive, image-processing techniques to allow the verification of CBCT to be automated. Discussions are in hand with CERN to secure a CERN Doctoral Student and with GSI (Darmstadt) to support a joint PhD programme.

Industrial engagement

The Centre's collaborations with MedAustron and Maxeler Technologies have been noted above. Discussions with Hamamatsu on the development of real-time dose-deposition imaging using the high-energy photons excited by the passage of proton or ion beams have been initiated. Communication continues with the National Physical Laboratory regarding dosimetry research. The Centre will host a half-day industry showcase, in autumn/winter 2018/19, to encourage engagement with industrial partners in the key areas of interest to the Centre.

Engagement with ISIS Department at the STFC Rutherford Appleton Laboratory

The Centre's accelerator-development activity is closely aligned with the R&D programme by which the ISIS Department at RAL seeks to deliver the capability required to upgrade the ISIS neutron and

Imperial College London

muon source. An MoU with the STFC is in preparation that will underpin a collaborative R&D programme of benefit to ISIS Department and the CCAP.

Seminar series

The Centre's seminar series began on 27th June 2018 with a presentation from S. Gruber (Medical University of Vienna). The programme for the autumn term 2018 is:

- 24th October 2018: Kevin Prise (Queens University Belfast); and
- 12th December 2018: Maurizio Vretenar (CERN)

Speakers have been approached for next term, the programme will be announced shortly.

Section 5: Research Highlights

Please provide a brief lay summary of the research activity undertaken since the Centre's approval, taking the opportunity to highlight any particular successes/achievements so that these may be further highlighted to stakeholders as appropriate.

Separately, please link relevant publications in Symplectic to the Group for your Centre. For guidance on the creation of Groups speak to your Faculty Web Officer.

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Over the year since its inception, the Centre has created programmes in three priority areas. These activities are summarised below.

1. Incremental development of improved radiotherapy techniques:

Cancer is the second most common cause of death globally. Local cancer control is of major importance to quality of life and overall chance of survival. RT is indicated in half of all cancer patients and is most commonly delivered using X-rays. In modern X-ray therapy machines the energy and intensity of the source is caused to modulate as it rotates around the patient. Variation of tumour position from day to day (due to breathing, changes of the filling of hollow organs, peristalsis, or more complex anatomical changes) is a major challenge. If not compensated, these variations cause imprecise delivery of the dose to the tumour and increased dose to normal tissue. Image-guided radiotherapy (IGRT) detects the tumour position immediately prior to treatment and allows for the adaptation of the dose if the target position has changed. This more precise delivery of radiation reduces dose to normal tissue, decreases the risk of toxicity, and may allow a safe increase in the dose delivered.

Centre personnel have reviewed the patient pathway and identified improving image processing in IGRT and the automation of the Cone-beam computed tomography (CBCT) process as a priority. CBCT is the state-of-the-art technology for IGRT. In this technique a flat-panel detector and a kilovolt radiation source are integrated into the X-ray-therapy machine. As the X-ray source rotates, multiple projection-images are acquired. Images are processed using a back-projection algorithm to produce a 3D image. The CBCT verification image is registered to the reference CT image, preferably by means of automatic image registration, to allow the position of the target relative to the planned position to be calculated.

Changes of the target position exceeding a pre-defined threshold are corrected online prior to the start of RT. Imaging, reconstruction and position correction requires about five minutes with commercial systems. This process adds to the patient-treatment time and requires manual input to acquire and then to match the CBCT images to the reference CT image. The quality of CBCT images are inferior to diagnostic images and interpretation of variations in soft tissue structures is problematic.

On the 4th October 2018 a proposal was submitted to the STFC for a CASE student to facilitate fast and accurate adaptive radiotherapy (RT) by automating on-treatment verification of CBCT scans. The PhD programme will be performed under the supervision of personnel from the CXH, Physics, the Dyson School of Engineering Design and Maxeler Technologies. The key goals of the project are the:

1. Specification of feature-recognition and tissue-classification metrics for the development of image-processing algorithms;
2. Development of image-processing algorithms on Maxeler low-latency, FPGA-based dataflow computing engines (DFEs); and
3. Clinical evaluation of the image-processing systems.

2. Development of novel, compact, laser-driven accelerator systems for clinical applications:

The energy deposited by X-rays falls exponentially with depth; i.e., energy is deposited in all tissues that lie between the point at which the beam enters the body and the point at which it leaves. As a result, for many important primary-tumour sites, the proximity of healthy organs places a fundamental limit on the photon-dose intensity that may be delivered. Proton and ion (hadron) beams overcome this fundamental limitation of X-rays because the bulk of the energy is deposited in the 'Bragg peak' that occurs as the beam comes to rest. This allows a large dose to be delivered to the tumour while sparing healthy tissue. These advantages have led to an increased emphasis on the provision of proton-beam therapy in the UK and across the world.

The maximum instantaneous dose that can be delivered is limited by today's proton and ion sources that produce ions at low energy (tens of keV). At such low energies the repulsion between the ions causes the beam to diverge rapidly and limits the capture efficiency. There is evidence that higher instantaneous doses may increase tumour control while improving the sparing of healthy tissue and decreasing treatment time. It is possible to overcome this limitation by using a laser to create protons and ions with energies up to one thousand times larger (10—20 MeV) and capturing them using a strong-focusing plasma (Gabor) lens.

The key technologies, i.e. the laser-driven source, the plasma lens, and the state-of-the art beam-transport technologies can be demonstrated in a low-energy facility capable of serving a systematic programme of radiobiology (see below). Therefore, over the past year, the Centre has:

1. Developed a first conceptual design of a 'Laser Accelerator for Radiobiological Applications' (LARA) that can deliver a 15 MeV proton beam to an end-station for in-vitro radiobiology;
2. Characterised the performance of a first prototype of the plasma lens required to capture the ions created in the laser-driven source; and
3. In collaboration with the MedAustron and the Medical University of Vienna (MUW), identified the key parameters of the in-vitro end-station.

3. First steps in the development of a systematic study of radiobiology:

Relative biological effectiveness (RBE) is the ratio of the dose of a reference radiation (typically X-rays) to the dose that must be delivered using proton or ion beams to achieve the same biological effect. RBE is known to depend on a variety of factors including particle energy, dose, dose-rate, tissue type, and ion species. A representative RBE value of 1.1 is used in proton- and ion-beam treatment-planning systems. A detailed, micro-biophysical understanding of proton-tissue interactions would allow enhanced treatment-planning systems to be developed that account for variations in RBE with ion species, tissue type, etc. A systematic programme of radiobiology is required to underpin the development of the requisite micro-biophysical understanding.

To initiate the Centre's programme in this area a collaboration has been forged with MedAustron and the MUW. The MedAustron facility includes three patient-treatment rooms and a fourth end-station dedicated to research. By establishing a collaboration with MedAustron and the MUW we have brought radiobiological expertise into the CCAP and now seek to become a contributor to cutting edge experimental proton and carbon-ion radiobiology.

A PhD student has been resident at MedAustron since May 2018. He has contributed to the commissioning of the carbon-ion beam through simulation and optimisation of magnet settings in the extracted beam lines. He has taken an active part in the data-taking programme. Having climbed the learning curve, he is now providing valuable feedback to the commissioning team. For example, he introduced Geant-based tracking codes to the simulation of the MedAustron accelerator facility and, using the tools he introduced, contributed to the re-evaluation of the beam-properties in the synchrotron. He will now contribute to the optimisation of the transfer line through which particles are brought into the treatment and research rooms.

Building on our successful collaboration with MedAustron, we are working with MUW to develop an instrumented phantom (the 'SmartPhantom'). At present, the energy deposited in cell cultures exposed to the beam in the non-clinical research room is inferred from simulations of the beam properties. Using the scintillating-fibre real-time dose-measurement system being developed using an STFC IAA grant as a basis, we are working with the MUW to develop a design for a SmartPhantom in which the dose to the biological sample is measured in real time, shot-by-shot.

The Centre is discussing the investigation of the impact of electron (micro-) beams at high dose rate and high energy (CXH, Physics, ICR). Two electron-linac based X-ray therapy machines will be taken out of service at the CXH in the near future. We plan to investigate whether these machines could be modified to provide the beams required for electron-beam research. We have also initiated discussion of the possible use of the electron accelerators at the STFC DL for this programme. A meeting jointly organised by the CCAP and DL will take place early in 2019 to discuss the electron-beam programme.

Section 6: Barriers to Success

Please describe any barriers or obstacles that the Centre has encountered that may prevent or slow progress of the Centre.

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Good progress has been made in the initiation of the multi-disciplinary activities and collaborations necessary to drive forward the Centre's programme. A total of 11 proposals have been submitted. Of these 6 had co-investigators from the Department of Physics and the Department of Surgery and Cancer. The ratio of the income from successful proposals to the value of the proposals submitted is 9%. Four 'high-value' (>£250k) bids were made. These included a bid for CRUK Multi-Disciplinary Award (£498.35k; CXH and Physics) with the title '*Laser-driven ion beams for radiobiology and treatment*'. In its feedback letter the CRUK indicated that the proposed work was more suited to the EPSRC Healthcare Programme. A revised proposal to the EPSRC is in preparation. The Centre is working to improve its success rate by: preparing to publish a conceptual design report on LARA that will demonstrate its feasibility and allow future funding bids to be set in context; establishing collaborations with key partners in the UK and overseas; and, through, for example, CASE-student applications begin to establish a track record.

In addition to the multi-disciplinary activities involving staff associated with the Centre, active collaborations have been established with MedAustron and MUW. These collaborations give Centre personnel access to cutting-edge, world-class facilities at MedAustron. By contributing first to the carbon-ion-beam commissioning, then to the instrumentation of the phantoms that will be used for proton and carbon-ion radio-biology, the Centre is poised to establish an experimental radiobiology programme unique in the UK. Perhaps the most valuable asset that the Centre has gained through these collaborations is access to leading academic and lab-based experts in medical physics and hadron-beam radiobiology.

The activities described above provide an excellent foundation on which the Centre can be built. A Business Case for the Centre is being developed in which the recruitment necessary to bring expertise to Imperial in the key areas of radiobiology and biophysics has been identified as a strategic priority. Discussions have therefore been initiated in the Department of Physics and the Department of Surgery and Cancer for the recruitment of:

- A lecturer in novel particle radiobiology (FoM/Dept. of Surgery and Cancer) with an interest in the development of a fundamental understanding of the radiobiology of novel particle beams and the application of this knowledge to improve clinical practice; and

- A lecturer in biophysics (FoNS/Physics) with an interest in the measurement, characterisation and modelling of the biological impact of particle beams.

These lecturers will join the Centre's multidisciplinary team, including its collaborators at MedAustron and MUW and its industrial partners, from the outset contributing significantly to a large-scale, clinically-focused project.

These appointments will strengthen the effectiveness of the CCAP cross-faculty programme; each lecturer will bring expertise and 'cultural awareness' from 'the other side'. In partnership, and led by clinical need, the lecturers will drive the development of:

- Novel accelerator, detector and imaging technologies;
- A fundamental understanding of the radiobiology of gamma, X-ray, electron, proton and ion beams;
- Model systems and codes that can be used by the wider radiobiology community; and
- Combined radiation, chemical and nano-particle modalities and automated treatment regimes.

Moving forward on this essential recruitment now has the potential to leverage investment from the Gunnar Nilsson Trust, which has indicated its readiness to provide 50% of the funds required to support the two lecturer positions.