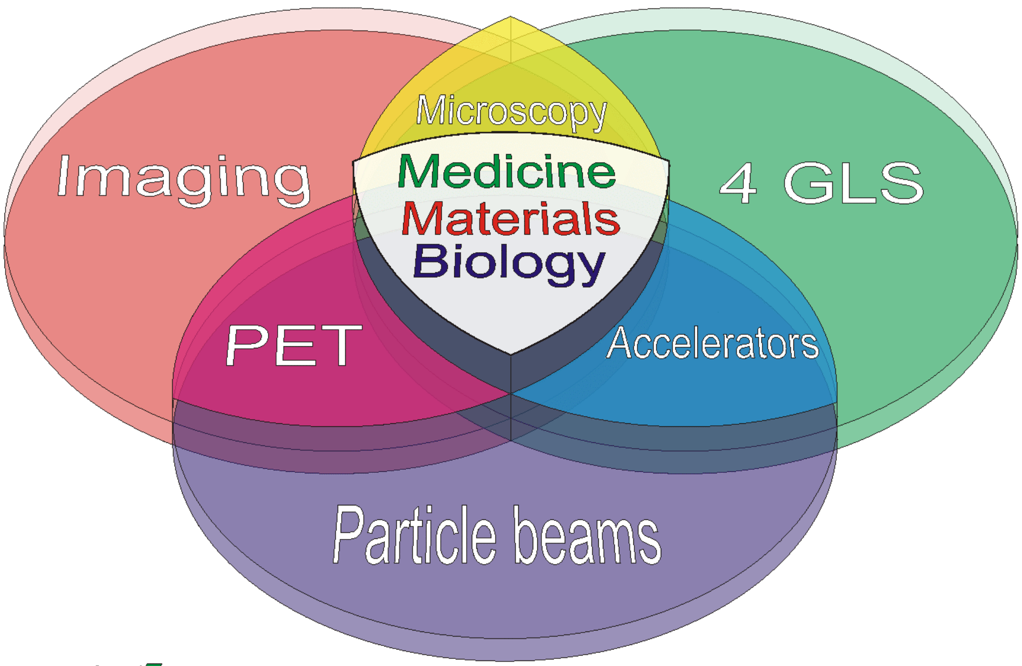
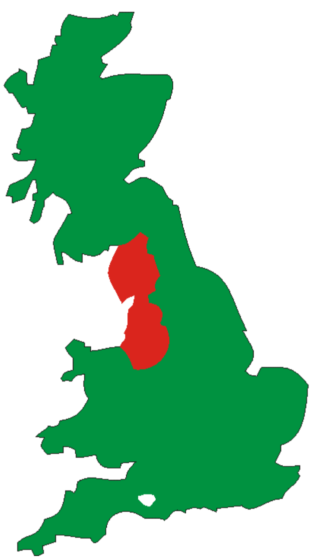
Centre for Accelerator Science Imaging and Medicine

CASIM





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UMIST
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Clatterbridge Centre for Oncology
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South Manchester University Hospitals
Royal Liverpool University Hospital
CLRC
National Nuclear Physics Community
National Infra-red Community

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Centre for Accelerator Science, Imaging and Medicine

We propose the establishment of a Centre for Accelerator Science, Imaging and Medicine (CASIM) at Daresbury, building on the existing infrastructure and expertise of the Laboratory and working in partnership with North West hospitals, universities and industry to enhance science in the region. The combination of intense proton beams, synchrotron light sources, free electron lasers and expertise in imaging technology available at CASIM will allow studies of topics ranging from the origin of elements in the universe to the detection of cancer at the molecular level. We will also develop new imaging technologies that will benefit the research work of the centre and revolutionise medical imaging. Developments in accelerator technology driven by CASIM and UK industry will allow strong UK involvement in future international science projects, such as the linear electron-positron collider. As a first step towards the establishment of CASIM, we ask that the North West Science Review (NWSR) provide funding for an infra-red free electron laser (£7M) and for developing medical imaging facilities (£4.7M). Initial estimates put the cost of the complete CASIM project at £160M to £170M and we request funding for a design study (£0.5M over three months) in order to resolve essential design parameters and provide accurate costings. We ask that the NWSR recommend the funding of the full proposal to the North West Science and Daresbury Development Group (NWSDDG).

Introduction

Advances in science, engineering and medicine are becoming increasingly dependent on accelerators, as is illustrated by the range of projects discussed in this proposal. The UK needs a focus to maintain and develop our expertise in accelerator science, to train new accelerator scientists and to exploit the possibilities offered by accelerators. CASIM will provide that focus by:

1) Designing, building and operating fourth generation light sources (4GLS) based on free electron lasers.

2) Developing and using novel imaging techniques.

3) Operating a proton accelerator for the production of short-lived isotopes for medical imaging and for the treatment of cancer and designing and building an accelerator for short-lived isotopes for research in nuclear physics.

The above projects provide the exciting long-term future for DL which are essential if the internationally renowned accelerator science group is to be maintained and students are to be attracted into the subject. In order to ensure that sufficient accelerator scientists are trained to satisfy the UK's future needs, several of the universities in the North West are developing M.Sc. courses in Accelerator Science in conjunction with DL. Ph.D. positions are being offered by two North Western universities.

This proposal is a collaboration between:

- Future users of the 4GLS including the national infra-red community, spokeswoman Dr. Andrea Russell, Southampton University and users of UV radiation, spokeswoman Prof. W. Flavell, UMIST.

- Medical, clinical and material scientists concerned with imaging technology, spokesmen Dr. Robert Lewis, DL and Dr. Peter Williams, NW Medical Physics.

- The national nuclear physics community, spokesman Prof. John Durell, Manchester University.

The proposal is co-ordinated by Prof. Peter Weightman of Liverpool University, and Liverpool University will act as lead organisation for the consortium.

Vice Chancellor Prof. P.N. Love
University of Liverpool on behalf of
all the collaborating organisations.

Some of the science programmes made possible by CASIM are described briefly in the following. Distinction is made between those which require full funding and the possibilities opened up by the funding requested from the NWSR.

Fourth-Generation Light Sources - 4GLS

The 4GLS free electron laser (FEL) complex will be a world-leading innovative and unique facility. It will provide radiation of unparalleled intensity from the far IR to the XUV, serving both the UK low energy research community and a wide range of industrial interests. Japan and the USA have already recognised the potential of FELs working in the IR and VUV regions; 4GLS will move the UK to the forefront of the technology and exploitation of these novel light sources.

Free electron lasers are the next generation of advanced light sources. An FEL relies upon a relativistic electron beam as its lasing medium, which provides a unique combination of tunability, coherence, polarisation, time structured pulses down to the ps range, and high laser power. They can span the spectrum from microwave to ultraviolet and potentially X-ray regions. All of these features are delivered with exceptional stability. The applications of FELs extend from pure scientific investigations of quantum effects to applied biomedical sciences in the treatment of cancers and other medical conditions.

The first FEL was demonstrated in 1977[1]. Since then there has been rapid growth in FELs around the world and there are now at least 27 facilities in operation in the IR and UV[2]. Of these several are well-established user facilities, including CLIO/Super-ACO (France), FELIX (The Netherlands), and the Stanford Free Electron Laser Center (CA, USA). UK scientists currently have access to the FELIX IR facility[3] via an EPSRC funded project. However, this project will end in the next 18 months and may then be renewed only annually. The access to FELIX is insufficient to satisfy the projected UK IR user community in condensed matter physics alone. The flexibility of the design proposed here will allow the IR-FEL to be used in its own right by a much wider community. However, the full power of the facility is realised in the combination of different types of radiation made possible by the 4GLS facility.

The 4GLS will contain three free electron lasers:

- An **IR-FEL** to generate radiation in the range 5 μm to 1 mm (microsecond pulses).
- A cavity based **VUV-FEL** to generate vacuum VUV radiation of energy 4-10 eV.
- A single pass (SASE mode) **XUV-FEL** to generate XUV radiation of energy 10 to 100 eV.

The technology to produce free electron laser radiation is here now *but* it is demanding. Making FELs work in the IR and VUV regions is already proven. In the XUV, the Tesla Test Facility[4] has shown that FEL radiation with energies up to 12.5 eV can be produced but for higher energies development work still needs to be undertaken. The IR and VUV FELs will be user facilities but the higher energy XUV-FEL is a development project.

The **IR-FEL** facility proposed here is an evolution of the designs already in operation at the FOM (FELIX) and Stanford University (SCA and FIREFLY). The basic components of an FEL are a magnetic undulator, electron beam and mirrors. As in the Stanford and FELIX designs we propose a two LINAC structure to provide IR light from 3 µm to 1 mm. The proposed design will enable simultaneous use of the FEL by multiple users as well as the innovative provision of variable polarisation of the mid-IR FEL output. The operating parameters of two operational FELs and the proposed FEL are shown below:

Parameter	FELIX	Stanford	Daresbury
Wavelength range	5 to 100 µm	3 to 65 µm	3 µm to 1 mm
Macropulse repetition rate / Hz	5	20	50
Macropulse duration	4 µs	3 to 5 ms	10 to 20 µs
Micropulse repetition frequency	1 GHz	11.818 MHz	1 GHz

The added value elements of the proposed Daresbury facility over the currently available user facilities are:

- The unique interactive possibilities between the lasers in the 4GLS;
- The provision of variable polarisation IR-FEL;
- The extent of multi-user access inherent in the design;
- The synergy with existing instrumentation and development expertise at Daresbury in accelerators and detectors;
- The interdisciplinary scientific culture offered by such a facility.

Summary of the scientific and technological opportunities of 4GLS

4GLS will offer unparalleled opportunities for the study of processes occurring on ultra-short time and length scales, in medicine, biology, chemistry, physics and materials science. The IR-FEL provides a unique facility in its own right with applications in imaging and microscopy, the study of cell metabolism, catalysis, phase separation and other fields detailed below. The full power of 4GLS is realised, though, through the combination of different types of radiation in this flexible source which opens up unexplored scientific vistas.

Pump-Probe Spectroscopy. Two-colour pump-probe spectroscopy offers an enormous range of possibilities in physics, chemistry, biology and engineering. One of the sources must be intense, in order to induce a change of state, and the second source probes changes in states coupled to the pump transition. This is an invaluable tool for probing excited states, which are often crucial for understanding of non-equilibrium systems, i.e. all systems that do useful work! Since the two sources have short pulses the changes may also be probed as functions of time, directly elucidating the dynamics. The 4GLS will be the perfect source for this, providing a unique combination of IR FEL, conventional synchrotron radiation, and VUV FEL. We mention briefly the variety of topics that can be explored. In semiconductor physics and technology a prime example would be the next generation of high speed (THz) frequency optical amplifiers, that will allow modulation of Terabit optical data transmission. There are also the new "spintronic" memories, involving spin-split conduction band states, where measurement of the memory time of the FIR-induced spin polarisation of optical excitons is needed. The study of **molecular fragmentation** as a result of photo-excitation or ionisation provides information on the way in which radiation is absorbed by a molecule and how the molecule disposes of the absorbed energy. Current experiments are limited to the study of just part of this process. Two-colour experiments in the VUV will transform this picture with the XUV laser used to ionise the molecule and the fragments identified using the VUV laser. These studies address issues that are fundamental to molecular structure, a necessary prequisite for understanding intermolecular reactions. In the biomedical sciences the effects of protein folding and single residue mutations on the vibrational energy transfer and dissipation[5] within biological systems may be investigated, and the synergy with the BBSRC structural biology centre at Daresbury will be important. Applications include photosynthesis and investigating the harmful effects of different wavelengths of sunlight on plants and animals.

Imaging and Microscopy. The high power, wavelength tunability and polarisation characteristics of the IR-FEL, coupled with recent advances in high resolution, 2D-detector technology, presents significant opportunities for IR imaging and microscopy. In the near/mid infrared, detector technology is well developed and via an established CLRC/Perkin Elmer collaboration, readout times of ~ 6 μs for a 27 mm^2 active area are possible. This collaboration could lead to a spinout company, as it presents significant opportunities for conventional commercial IR sources also. Recent developments in scanning near-field infrared microscopy (SNIM) present a method of extending the spatial resolution of the instrument beyond the diffraction limit of the IR-radiation (~ 5 μm). Traditional scanning tip methods have limited data collection rates to ~1 minute per image, but the "tipless near-field spectroscopy" technique[6] has overcome this and data acquisition rates of 40 ms per image are possible. The powerful combination of IR-FEL, advanced detectors and SNIM presents a unique scientific opportunity for new areas of chemistry, physics, biology and medicine. **VUV confocal microscopy**[7] will allow time-resolved structural studies on organelles and sub-cellular structures in cell and tissue cultures at spatial resolutions < 100 nm. This is important to the pharmaceutical industry and to the development of connections between organic and semiconductor systems. The development of **evanescent wave microscopy**[8] has the potential to study single molecules on the surface of the cell in real time.

Cell Metabolism. The effects of drugs on cell division will be studied dynamically by tuning to chemically specific bands within drug molecules. The exact delivery of drugs to target sites within the cell will be investigated and simultaneous FEL-IR pump and synchrotron-IR probe measurements will facilitate simultaneous imaging of the drug and cellular protein amide I band. This research is vitally important for the screening of new drugs by pharmaceutical companies prior to clinical trials and will exploit existing expertise at Daresbury in cell culture and IR imaging of live cells and histological tissue sections[9].

Combinatorial Chemistry and Enzymatic Catalysis. The rapid development of fabricated microstructures such as "lab-on-a-chip" present novel opportunities for imaging with the IR-FEL. By immobilising a combinatorial library of enzymes on the chip, it will be possible to chemically image the plate as reactants flow over the surface. This will allow high throughput screening of enzyme activity and build on the unique capability of Daresbury scientists to model microfluidics.

Phase Separation and Flow Birefringence. The linearly polarised IR will be used to monitor flow birefringence, for instance in foods such as yoghurt, chocolate, etc. as they are extruded through pipes. The induced stress in the molecules can be monitored via the degradation of the amide bond under flow.

Ballistic Imaging of Patients. IR/VUV-FEL light offers the exciting prospect of imaging tissue to a resolution of a few μm. This technique relies on the short pulse structure and high intensity of the FEL, as the small proportion of ballistic photons that pass straight through tissue without being scattered have to be separated from the majority that are scattered. The scattered or diffusive photons blur and distort the image but can be rejected by a fast shutter, because they take fractionally longer to reach the detector. A shutter fast enough to accomplish this (Kerr gate) has recently been developed by CLRC. This technique would provide high resolution structural images to complement, for example, PET functional images.

Ablation and Surface Modification. The high peak power, tunability, and pulse structure of the VUV and IR FEL output enable their use in the modification and creation of novel surfaces, for example by ablation, photon-induced polymerisation or selective recrystallisation. In polymer processing, for example, the FEL can be tuned selectively to the carbonyl absorption band for PET or nylon, thus imparting ordered surface structure on a dimensional scale of 5 to 10 μm. In dentistry, FEL output at $\lambda \sim 9.4$ μm, in resonance with the PO_4 coupling bond of hydroxyapatite, can be used to polish and surface-harden teeth.

'Laser Scalpel' Surgery. In the USA, surgeons have recently used an IR-FEL to remove a tumour from the temple of a human patient[10]. The advantage of using the FEL over other lasers is that less thermal damage is done to the surrounding tissue, providing a cleaner cut and less collateral damage. Selective removal of cholesterol esters associated with atherosclerosis has also been demonstrated[11]. FEL output has also been shown to be useful in repairing corneal tissue and in wound healing[12]. The multi-user nature of the IR-FEL facility would make treating patients a realistic prospect.

Ultra-Fast Time-Resolved Structural Studies of Proteins, Nucleic Acids and Carbohydrates. FEL technology has the potential to reveal the process by which the linear chain of amino acids folds into the 3-D structure of a functional protein, helping structural genomics and understanding of diseases of mis-folding such as Alzheimer's, cystic fibrosis and CJD. A VUV-FEL will provide the first access to the peptide absorption bands between 150 nm and 230 nm for nanosecond studies, the right wavelength and timescale for these problems. **Nanosecond VUV circular dichroism** will provide dynamic information on formation of the different types of helices, parallel and antiparallel beta structures, and the many types of beta turns of a protein. **Nanosecond VUV resonance Raman**[13] will for the first time allow us to distinguish the role of chromophores of amino acid side chains in folding[14]. The IR-FEL will provide direct nanosecond circular dichroism vibrational mode information of proteins to complement these studies. Combining circular dichroism and Raman spectroscopy provides measurement of **Raman optical activity**, a powerful technique for ensuring enantiomeric purity in drugs[15].

Astrophysics. The high intensity of the XUV-FEL will enable spectroscopic measurements on radioactive species and non-naturally occurring isotopes generated by the proton cyclotron. Almost nothing is known of the absorption spectroscopy of these species, highly relevant to our understanding of stellar atmospheres and interstellar clouds. The information gained will thus help to shape our ideas about the origins of the universe.

Nanoscale Materials and Nanocluster Research. The feature size on semiconductor chips has reduced logarithmically for three decades. In order to meet the current 'road map' of the industry standard to be achieved by 2003, knowledge and control of dopants on a nanometre scale is needed. Similarly, there is an urgent requirement to understand better the transient characteristics of device structures. The output from 4GLS offers unparalleled opportunities for the highly spatially and time-resolved studies necessary from these often dilute systems. For example, pump-probe experiments using the VUV FEL and undulator radiation allow studies of electron-hole pair recombination dynamics in semiconductors including the transient behaviour of Schottky diodes and nanoporous materials such as porous Si and TiO_2 (used in photovoltaic cells and display devices). Free electron lasers will revitalise the field of photoemission by enabling the electronic structure of these materials to be probed with unprecedented angular and energy resolution and at ultra-dilute concentration. For example, a VUV-FEL will realise the goal of wide-band **VUV and XUV photoemission measurements on <u>free</u> clusters** in the size range 1-5 nm. These clusters are exciting because they mark the boundary between molecular and solid state systems, but have properties distinct from both.

Magnetic Phenomena. Spin electronics is a new and rapidly developing field with the potential to supplant silicon technology. However, realising this potential will require the increased photon flux of the VUV- and XUV-FELs to enable high-resolution studies of the spin-dependent electronic structure of materials. Magnetic characterisation by optical methods is complementary to the photoemission methods described above and the 4GLS FELs open the way for application of both linear and non-linear methods such as magnetic second harmonic generation (MSHG) and non-linear magneto optical Kerr effect. These techniques are particularly attractive for the study of industrially relevant thin films and interfaces. The continuous tunability and high intensity from the FELs will also enable both sum/difference frequency experiments and resonant measurements.

Coherence. The XUV and VUV-FELs will have a high degree of spatial and temporal coherence, ideal for imaging purposes such as holography. An unprecedented resolving power ($> 10^6$) will be achievable by the use of Fourier transform spectroscopy[16], providing resolution at the rotational level in the VUV. The use of conventional laser sources in photoionisation spectroscopy has led to the discovery of the influence of the ponderomotive potential of the electron[17]. This intriguing effect, with its relevance to modelling of laboratory plasmas and stellar atmospheres, is an obvious candidate for study by the higher energy, coherent radiation from the XUV-FEL.

Industrial Applications of 4GLS technology The industrial potential of FELs has been recognised in Japan and the USA where consortia have been established to exploit and develop the emergent technology. The Free Electron Laser Institute (FELI) in Osaka[18] promotes research on fundamental technologies in the private sector and is working on projects that include development of TeraHertz band super high speed optically-controlled modulating elements; creation of new materials by selective excitation of molecular vibrations; development of new process/altering technologies by selective molecular excitation. Similarly the Laboratory of Advanced Science and Technology for Industry has been established at the Himeji Institute of Technology to exploit combined FEL/SR technology in a facility (New Subaru) being built on the Spring-8 site. In the USA a consortium[19] of major US firms (DuPont, 3M, IBM, Xerox, AT&T), universities and the Thomas Jefferson National Accelerator Facility has been formed to use 4GLS technology for industrial processing applications such as surface modification of polymer film, fibre and composite products; micromachining and surface finishing of metals, ceramics, semiconductors and polymers; materials analysis, characterisation and non-destructive testing.

The North West Universities and Daresbury Laboratory already have the expertise to develop the technology required and a similar model will be instigated to nurture industrial involvement in the North West and extending eventually throughout the UK.

Proven areas of strength with clear industrial potential in the UK include: clusters for catalysis and microelectronics; nanostructures; spin dependent characterisation techniques; microwave plasma technologies for cutting and processsing; telecommunications; information storage. The Industrial Free Electron Laser (IFEL) Group at Liverpool University is home to a microwave FEL aimed at industrial applications[20]. IFEL is currently addressing problems in the areas of plasma production for metal cutting, welding and cleaning, underwater communications and imaging, water sterilisation and industrial chemistry. Collaboration between the 4GLS and IFEL groups will ensure that the technical, design and applications expertise at both centres is exploited with maximum efficiency.

The SRS

The SRS will operate for seven years after which it will be replaced as the UK's research synchrotron by DIAMOND at the Rutherford Appleton Laboratory. It will be sensible to examine the ways in which the future operation of the SRS can contribute to developments in the 4GLS proposed here.

Request from the North West Science Review Team

The IR-FEL is ready to start construction now, and we seek funding now from the NWSR of £7M to build the IR-FEL facility, including 100 MeV linac and four end stations. We also seek immediate funding of £0.25M for a three-month design study that will provide the detailed engineering layout and a costing for the total project. For guidance purposes only, we envisage the 4GLS consisting of a two-stage linac, half of which feeds the 'SASE' XUV-FEL with the second stage feeding a 600 MeV storage ring containing the VUV-FEL. The total cost of the 4GLS facility is likely to be around £60-70M.
We ask the NWSR to recommend the funding of the full proposal by the NWSDDG.

Imaging, Radiological Science and Technology

Imaging is a priority area of 21st century biomedical research for universities, the NHS, research institutions and the drug industry. The NW research community aims to be at the forefront of developments in imaging science and is committed to advancing the application of molecular imaging in medical research.

Our Background

We intend to build upon the strong imaging expertise already located in the North West. For example:

- Daresbury instrumentation group is internationally respected for detector advancement, notably high-speed imaging. It works closely with local university groups and others, e.g., advanced imaging with the *Foresight Initiative* supported *IMPACT* programme (includes UMIST).
- The Manchester Positron Emission Tomography Centre (*ManPET*) is a multidisciplinary partnership in biomolecular imaging, which serves as a model for successful cross-institution interaction. *ManPET* has established an internationally competitive research programme that is clinically and biologically driven. It will be further enhanced through the additional instrumentation expertise offered by collaboration with the Daresbury Instrumentation Group.
- Manchester Medical School is part of the EPSRC interdisciplinary research collaboration 'From Medical Images and Signals to Clinical Information'. This £12M, five year programme involves the University of Oxford, UCL and KCL
- The Christie and Clatterbridge hospitals are two of the nation's premier oncology centres, with substantial clinical imaging expertise. The Walton Centre for Neurology & Neurosurgery (WCNN) has an international reputation in neuroscience whilst the Royal Liverpool University Hospital has excellent nuclear medicine expertise.
- The existing well-founded centres of excellence within the North West contributing to this proposal include:

Centre	Relevant Expertise
Daresbury Laboratory	Radiation detectors and instrumentation, radiation physics, synchrotron radiation Data processing, image analysis, etc., high performance computing, GRID
UMIST	Instrumentation , analytical science, imaging, image processing, radiochemical targeting, image engineering, synthetic- and radio-chemistry, analytical science molecular biology, biological modelling, genomics & proteomics, materials science
Liverpool University	Silicon detectors, magnetic resonance, image analysis
Walton Institute	Neurology, neurosurgery
ManPET	Image production & processing, biochemical targeting, radiotracers, radiochemistry, pharmacology
University of Manchester	Image analysis, computer vision, neurology, MR, osteoporosis, materials science
South Manchester Hospitals	Mammography, nuclear medicine, sentinel node analysis
Christie Hospital	Clinical research into novel therapeutics, Image production & processing image guided radiotherapy
Paterson Institute for Cancer Research	Biochemical targeting, radiotracer technology, target-specific therapy, translational research, drug development, cancer biology
Salford University	Civil engineering, materials
Clatterbridge Hospital	Proton therapy, clinical research into novel therapeutics, medical oncology image production & processing
Royal Liverpool Hospital	Medical physics, nuclear medicine, image production & processing

Aims

To provide a clinical focus we intend to concentrate on two disease classes, neuroscience and cancer. In oncology, for which the treatment aspects are an essential element of other aspects of this proposal, the importance of imaging is enormous. An identified ultimate aim is to develop rapid 3-dimensional time-resolved molecular imaging at resolutions down to sub-micron levels. The ability to perform such imaging *in vivo* would revolutionise disease diagnosis and also subsequent therapy. Modern therapeutic interventions such as linear accelerator based stereotactic radiosurgery and focal delivery of potent drugs into diseased areas are only possible with the 3D identification of the target. Advanced imaging is vital to monitor the effect of therapy, detect pitfalls and design new treatment strategies. Our proposed beamline and associated instrumentation will provide the first steps to this goal. It will provide radical advances in its own right and will permit the development of skills for longer-term development to exploit the even more exciting capabilities of the 4GLS and IR FEL e.g. superior X-ray imaging using Compton scattering.

The central nervous system (CNS) exhibits the most complex structure-function relationships within biology. It is here that future molecular imaging, e.g. PET, will need to be combined with imaging of functional systems within the CNS. Diagnostic precision in detecting abnormalities of function and tissue characteristics, e.g. localising the epileptic focus, will need to be allied to similar precision in the delivery of a range of therapies including drugs, surgical ablation, stimulation and immuno-therapies. Here there is tremendous synergy between this imaging network and the proposed proton therapy centre.

The ability to work in the micron spatial regime will open new fields of life sciences study and allow the study of pathologies currently beyond the scope of computed tomography (CT) machines. The new instrument will make possible non-invasive imaging of delicate structures in their native 3D relationships, contrasting with current techniques, which distort specimens and destroy vital information. Examples involving the work of leading NW scientists include the work at Whiston Hospital to develop understanding of finger joint operation, genetically induced defects in embryos and 3D structures of insect neural systems. Of immense importance will be the addition of coherent scatter CT (CSCT) and fluorescence techniques, which will allow elemental and molecular structure maps to be produced. Important examples include the role in osteoporosis of bone trabecular structure and mineral distribution, a major interest at Manchester Medical School .

Initial Roadmap

To start forging our comprehensive imaging network, we have identified two areas that will make an immediate impact on scientific advancement, health care and commercial opportunities: PET and advanced X-ray imaging. Supporting these will be the creation of a dedicated group of instrumentation scientists and engineers at Daresbury with the specific remit of developing medical instrumentation. This group will be unique in having access to advanced facilities, whilst being fully integrated into the NW clinical network via joint appointments. It will be responsible for the programmes detailed below.

Dedicated imaging beamline on the SRS

Recent experiments at Daresbury have demonstrated that exploiting the characteristics of *scattered* radiation is now set to take X-ray imaging onto a new level. We propose to combine synchrotron radiation from one of the SRS superconducting wigglers, radical detector development and advanced statistical signal processing to produce a world-leading imaging beamline which will take full advantage of directly transmitted, diffracted and secondary photons over the range 4 – 80 keV.

It will be capable of exploiting refractive effects to produce images of extraordinary contrast (DEI)[21] and will enable us to progress further studies of the tenfold reduction in dose over existing clinical techniques already achieved by partners in this network[22]. This combination means that the feasibility of the technique for screening young women at high risk of breast cancer could be investigated. The detection of scattered as well as transmitted X-rays creates molecular structure sensitive images. Recent data clearly demonstrates that malignancy can be detected using only scattered X-rays[23,24]. Moreover, changes in tissue structure over several centimetres lead to the possibility of detecting very small tumours. The full potential can only be realised with associated radical detector development. We will therefore strengthen the existing collaborations between Daresbury and UMIST by adding the *Liverpool Silicon Detector Centre* to create a world-leading X-ray detector development consortium. In order to transfer the technique into the clinic we will work closely with the Philips Medical Imaging coherent scatter computed tomography project to develop a practical scanner for hospitals. Philips are likely to make a initial contribution to the programme of £20k.

The proposed beamline will incorporate micro-tomography (μCT) and the combination of fluorescent and diffraction modalities within a single instrument will enable concurrent elemental and structural analysis. New composite materials with structural elements covering several orders of magnitude will be studied for the first time. For example, polymer composites are being introduced into the wing set of the European Airbus yet very little is known about the cumulative effects of impact damage. We will be able to non-destructively visualise the damage, thus facilitating the monitoring of the evolution of impact damage during fatigue cycling[25,26]. By combining complex sample environment, e.g. tomographic imaging with strain measurement, complete characterisation of failure mechanisms will be possible – the potential of which has already been demonstrated by the proposers. However the procurement of μCT facilities is outside the financial capabilities of industry. The availability of a national central facility would overcome this restraint giving competitive advantage to UK companies, especially those in the North West. As a first step, a laboratory-based system is being installed in the new JIF funded Unit for Stress and Damage Characterisation in the University of Manchester/UMIST Materials Science Centre. A new instrument at Daresbury will complement the capabilities of the USDC facility (with staff secondment), exploit local expertise in x-ray instrumentation, data analysis and visualisation to establish the NW as a focus for UK engineering X-ray imaging.

The proposed SR-based instrument will exploit the synergies between material and medical science needs, to allow much finer resolution scales than possible on laboratory sources – both spatially and temporally. In collaboration with Philips we will develop novel x-ray sources to transfer this technology into hospitals and industry.

Biomolecular PET Imaging

Biomolecular imaging is becoming a vital component of biomedical science with a pivotal role in the translation of laboratory-based research into human studies. PET imaging is a powerful way of studying biochemical processes at the molecular level in-vivo and in real time. PET offers the potential to provide new insights into disease mechanisms and the effectiveness of target-specific therapy.

Small Animal PET

Modern molecular and pharmacogenetic research demands the need for non-invasive imaging systems with much higher spatial resolution and sensitivity than has been developed to date[27]. It is necessary to develop systems for fully quantitative studies of real-time biochemical processes in small animals. We therefore propose to:-

1. Establish a state-of-the-art quad-HIDAC PET camera at UMIST to enhance our *in vivo* biochemical imaging capabilities. Its performance will be enhanced by developing novel 3D image reconstruction algorithms and it will also allow us to determine the research focus for the next generation of PET systems.

2. Design a novel small animal PET camera having both high sensitivity and spatial resolution in collaboration with PerkinElmer. Two concentric cylindrical arrays of detectors having demountable end-caps, will be fabricated from germanium. Using a Compton camera configuration, the direction and energy of the gamma rays can be determined, as well as position. This will allow the use of scattered events thereby including a greater proportion of the total emissions in the image reconstruction, and dramatically improving the sensitivity. The projected count rates of 10^8 per second require fast asynchronous event processing, for which the Daresbury instrumentation group is internationally renowned. This will enable true 4D PET to be fully realised.

Sentinel node analysis

We also intend to pursue, in conjunction with Electron Tubes Limited and Manchester Breast Screening Centre the development of a compact detector to allow the accurate identification of the sentinel node in breast cancer. This is set to become the technique of choice to determine metastatic spread and whilst this is only a small project, it represents the kind of development that CASIM makes possible. Electron Tubes will donate much of the necessary equipment for the prototype.

Request from the North West Science Review Team

We seek funding for the first stage of this project from the NWSR of £4.7M, comprising £2.5M for the imaging beamline on the SRS, £0.5M for the quad-HIDAC development, £1.5M for the small animal PET scanner and £200k for the sentinel node detector. The later developments will require further funds estimated at £20M. This will provide three small cyclotrons at strategic points throughout the region to enable exploitation of the PET developments; development of the advanced scanner technology for human use; a facility to take advantage of isotope production from the radioactive beams facility; and staff, including joint appointments, to take forward these developments.
We ask the NWSR to recommend the funding of the full proposal by the NWSDDG.

Beams for Basic Science and Medical Applications

We propose to construct a unique, world-leading facility providing multiple beams of radioactive ions for nuclear physics, nuclear astrophysics, materials, bio-medicine and environmental studies. In parallel with these research goals, the installation will constitute a major upgrade to the clinical and isotope production activities currently undertaken at the cyclotron of Clatterbridge Hospital and will take over these operations as soon as the first phase of the installation is completed.
The proposed facility will put the UK in the forefront of the current global thrust towards radioactive beam accelerators for nuclear physics research. It has only recently been realised that it is technically possible to accelerate not only stable nuclear species but also unstable, radioactive ions. This represents a major advance in the field of

nuclear physics and opens up radical new possibilities in other disciplines. However, the development of such facilities is in its infancy and there is as yet no example worldwide capable of delivering intense beams of a wide range of radioactive nuclei at the energy of the Coulomb barrier where nuclear reactions reveal most about the quantal states of the nucleus.

The concept here is to generate beams of a wide range of radioactive species using a high intensity (> 100 μA) beam of 230 MeV protons from a cyclotron. For neutron-rich nuclei, the primary reaction would be direct fission of a ^{238}U target; in excess of 10^{14} fissions/sec could be produced, making this a world-leading facility for this class of nuclei. On the proton-rich side of stability, a variety of targets and light-ion reactions would allow access to the full range of species available. Extraction of the ions from the target/ion source will be based on the technology developed over many years at CERN-ISOLDE and, more recently, in collaboration with CLRC. Re-acceleration to 10 MeV/A will be achieved with a superconducting linear accelerator. The result will constitute a next-generation facility in terms of the breadth of beam species, intensities and final energy achievable. The current initiative offers the opportunity for the UK to provide the leading facility of its kind in Europe and indeed the World.

Basic Science Research

In nuclear physics beams of radioactive nuclei will allow us to address some of the most crucial outstanding questions in the field. They will allow us to explore the absolute limits of existence of nuclei. At present we have little idea, for example, of how many neutrons we can add to the nucleus before it becomes unstable to neutron emission in its ground state. Our theories suggest, however, that as we continue to add neutrons, we may encounter radically new phenomena associated with the skin of neutrons building up on the outside of the nucleus. Indeed, this will be our best chance to study pure neutron matter. Nor do we know how heavy a nucleus can be. We have managed to create small numbers of atoms of the heaviest elements but it seems likely that we can add only a few more elements with stable beams. Again, theory points to quantum shell structure in nuclei near proton numbers 114 and 126, that gives extra stability against spontaneous fission. With beams of neutron-rich nuclei we can first explore and understand the mechanisms of reactions leading to such nuclei: then we can start to produce them.

Although motivated primarily by developments in nuclear physics, this will be a multidisciplinary facility. It will offer multiple beams of the same range of radioactive ions at several energies. For instance, some of the beams created will open a doorway to nuclear astrophysics. The energy that stabilises stars, and makes them shine, has its origins in nuclear reactions involving the fusion of nuclei. In these processes the chemical elements up to iron are made. Beyond this the elements are thought to be created in violent and explosive events such as novae, gamma-ray bursters and supernovae. Increasingly, telescopes allow us to observe the elemental abundances for individual astronomical objects but to understand these abundances requires much more information concerning reactions involving unstable nuclei. The only way to obtain this information is with beams of radioactive nuclei.

Quite apart from its intrinsic interest the atomic nucleus provides a unique laboratory for tests of various fundamental interactions and the standard model of particle physics. For example, Feynman and Gell-Mann introduced the conserved vector current (CVC) hypothesis in the theory of the weak interaction. The best test of this theory comes from the strength of superallowed β decays in specific nuclei. Beams of stable nuclei have allowed us to measure some of the relevant nuclei but we are left with uncertainties in the small corrections that must be applied to the experimental values. The production of heavier nuclei in sufficient intensity will allow the proton number dependent, systematic variations in the corrections to be determined.

Beams of radioactive nuclei will also be of great value in materials science. The decay properties of radioactive ions implanted into solids are modified by, and hence reveal the nature of, their environment on the microscopic scale. In this sense the ions act as "spies" on their environment and studies of how their decay is modified using techniques such as perturbed angular correlations, Mössbauer spectroscopy and emission channelling reveal the nature of that environment. Radioactive decay also involves chemical transformation and this can provide a unique chemical signature at the atomic level. Many standard spectroscopic techniques such as photo-luminescence spectroscopy, capacitance voltage, electron paramagnetic resonance, photo-reflectance and deep level transient spectroscopy are all chemically blind and generally rely on an educated guess about the chemical nature of defects and impurities. These techniques can be cured of this blindness if the signals are from known radioactive implants.

Intense beams of mono-energetic positrons can also be produced, controllable in the range 1eV-400keV, and several orders-of-magnitude more intense than positron sources currently available in the laboratory. This would allow a large range of studies of subsurface regions, interfaces, thin films, surface spectroscopy, microscopy and atomic physics to be pursued.

This proposal builds on the existing programme being carried out by the UK Nuclear Physics community at overseas laboratories, in which a considerable amount of money has been and is being invested in equipment. It is foreseen that much of this equipment will be returned to the UK to be installed at the proposed facility. Further instrumentation will be provided from grant requests to EPSRC during the period running up to the radioactive beam facility going online.

The fact that the facility will be world-leading means that collaborators from continental Europe will make significant contributions to the instrumentation of the laboratory[28].

Medical Therapy

The choice of a 230 MeV proton cyclotron as the driver accelerator also provides the basis for a proposed proton radiotherapy centre. Such a centre will be a world-class medical research facility. It will:

- Extend the role of proton therapy in the UK, exploiting the higher proton energies available.
- Provide a facility linking fundamental science at Daresbury with clinical research throughout a network of leading medical centres in the North West.

The 62 MeV proton therapy facility at Clatterbridge Centre for Oncology (CCO), the only medical proton treatment facility in the UK, has been largely limited, by the restricted particle range, to research into the treatment of ocular tumours. The higher energy proton beam required for nuclear physics research can be used to treat deep-seated tumours such as spinal chordoma and chondrosarcoma, where proton therapy, at the leading edge of clinical oncology, is widely accepted as the treatment of choice[29,30,31,32]. Other tumours that are adjacent to critical structures may also benefit from proton therapy and clinical research needs to be undertaken to determine optimal treatment techniques and to establish the treatment efficacy[33]. Comparisons with other developing treatments such as Intensity-modulated radiotherapy (IMRT) will be a necessary part of this research that will be carried out in association with other specialist centres in the North West, building upon the specific strengths in each centre.

Research into neuro-oncology is seen as an early priority, providing a model for feeding future research through to service development. This research will explore the radiobiological and physical rationales for treatment of intracranial tumours using different radiotherapy modalities, including proton therapy. It will build on the combined experience of Walton Centre for Neurology & Neurosurgery (WCNN) and CCO in proton therapy, linear accelerator-based stereotactic radiotherapy, and interstitial radiosurgery using both radioactive iodine seed and photo-electron brachytherapy. As part of the programme of research, specific objectives will be to develop predictors of tumour response based upon metabolic, physiological and molecular parameters determined by studying normal tissue and tumour biology using PET, MR, and genetic analysis of stereotactically-biopsied tissue. Such research interfaces with existing work on functional imaging carried out in association with the Magnetic Resonance & Imaging Analysis Research Centre (MARIARC), with molecular research carried out in association with Clatterbridge Cancer Research Trust (CCRT), and with the advanced imaging facilities envisaged as part of the CASIM proposal.

Proton beams for therapy will be provided alongside and without compromising other applications, including nuclear physics and isotope production. Development of a proton therapy programme fits synergistically with expertise readily available at Daresbury, drawing upon specialist skills in imaging, electronics, beam control, computing, and engineering.

The proposal provides an opportunity for radiotherapy research using high-energy proton beams which is unique within the UK. The research programme combines clinical, laboratory science and medical physics expertise which, critically, is available only within the North West at CCO and CCRT, WCNN, CH-NHST and PICR, and University of Liverpool. It builds upon existing research interests of these centres, will act as a driver for future research across a broad scientific and clinical base, and integrates with developments proposed within the Universities of Manchester, UMIST and Liverpool.

Request from the North West Science Review Team

We seek funding of £0.25M from the NWSR for a design study, to be carried out over a period of three months. This will provide the detailed engineering layout and a costing for the total project. This is estimated to be around £80M (including VAT), comprising approximately £65M for the facility, £5M for instrumentation for the nuclear science programme, £7M for the medical therapy programme, and £3M for specialist facilities at the Walton Centre for Neurology & Neurosurgery.

We ask the NWSR to recommend the funding of the full proposal by the NWSDDG.

Strategic North West Industrial Development

This proposal will contribute significantly to the North West Development Agency's vision for the region. A number of collaborations and formal contractual relationships already exist between Daresbury, NW Universities and NW businesses in eleven out of fourteen of the established and target sectors identified in the NWDA strategy (see back cover). A key factor is the significant strength of existing activity in the target areas of life sciences and medical equipment and technology.

Financial support for this proposal has already been given from several interested industrial partners. These include:

Perkin Elmer Instruments (UK) Ltd. – £0.25M for development of Ge detectors for microPET.

Philips Medical Imaging – £20K for development of Coherent Scatter Computed Tomography.

Electron Tubes Ltd. – Provision of instrumentation for sentinel node analysis.
Manchester Innovations Ltd. – reciprocal arrangement between MIL and Daresbury is being established whereby MIL will offer SR facilities to potential start-up companies. Daresbury fully supports the MIL proposal to establish a Core Technology Facility on the BioIncubator site.

Summary

This proposal describes several linked projects across a broad range of science in the North West which build on the strengths of the work force at the Daresbury Laboratory, boost economic regeneration and enhance the science base in the region.

References

[1] D. Deacon, L. Elias, J.Madey, G. Ramian, H. Schwettman and T. Smith, Phys. Rev. Lett., 38 (1977) 892.
[2] J.M Ortega, Accel. Based IR Sources and Applications, G. Lawrence Carr, P Dumas, Ed, Proc SPIE 3153 (1997) 2.
[3] D.Oepts, A.F.G Van der Meer, P.W. Vanamersfoort, Infrared Phys Techn 36 (1995) 297.
[4] "A VUV Free Electron Laser at the TESLA Test Facility at DESY" Conceptual Design Report, DESY, 1995, TESLA-FEL 95-03. Tesla-FEL lasing at 109 nm. http://sbfel3.ucsb.edu/www/desy1.html.
[5] G S Edwards, B. Johnson, J. Tribble and K Wagner, Optical Engineering 32 (1993) 314.
[6] D V Palanker, G M H Knippels,T I Smith, H A Schwettman, Optics Comm., 148 (1998) 215.
[7] Handbook of Biological Confocal Microscopy. Ed James B. Pawley, Plenum Press 1995.
[8] Y. Sako *et al* Nature Cell Biology (2000) 2: 168-172.
[9] M J Tobin, M A Chesters, M Pearson, N R Griffin, S E Fisher, B. Ruzicka, Accelerator Based Sources of Infrared and Spectroscopic Applications, G. Lawrence Carr, P Dumas, editors, Proc SPIE 3775 (1999) 96.
[10] Vanderbilt University press release, December 20th 1999.
[11] K. Awazu, A Nagai, T. Tomimasu and K. Aizawa, Nucl. Inst. Meth. B144 (1998) 225.
[12] M. Ostertag. KC Schmiedt J M Ortega, M. Bende and B Jean, Investigative Ophth. & Vis. Sci. 37 (1996) 2625.
[13] D. Clarke *et al*, Proceedings of the National Academy of Sciences (1999) 96, 7232.
[14] Y. Guan *et al*, p. 276-321, in Analytical App.s of Raman Spectroscopy, Ed M.J. Pelletier, 1999, Blackwell Science.
[15] Michael J. Pelletier, 'Introduction to Applied Raman Spectroscopy', in Analytical Applications of Raman Spectroscopy, Ed M. J. Pelletier, 1999, Blackwell Science.
[16] A P Thorne and M R Howells Vacuum Ultraviolet Spectroscopy II, ed J A Samson and D L Ederer (Academic Press, New York, 1998) p73.
[17] R R Freeman, P H Bucksbaum, W E Cooke, G Gibson, T J McIlrath and L D van Woerkom, Atoms in Intense Laser Fields, ed M Gavrila (Academic Press, New York, 1992) p43.
[18] Free Electron laser Institute, FELI: http://gatekeeper.feli.co.jp/English/.
[19] Laser Processing Consortium, LPC: http://www.jlab.org/FEL/.
[20] A. Shaw, A. Al-Shamma'a, R.A. Stuart, C. Balfour and J. Lucas, Nucl. Inst. Meth. Phys. Res., A, 375 (1996) 245.
[21] Chapman D, et al Diffraction enhanced x-ray imaging *Phys. Med. Biol.* **42** 2015–25 (1997).
[22] R.A. Lewis et al *Synchrotron Radiation News Vol. 12, No. 1 pp. 7-14* (1999).
[23] R.A. Lewis et al *SPIE **Vol. 3770**, 32-37* (1999).
[24] R.A. Lewis et al *Journal of Synchrotron Radiation In press, accepted July 2000.* (2000).
[25] Kornblum et al, *Nature Biotech*, **18**: 655-660, 2000.
[26] E. Maire, R.A. Owen, J.-Y. Buffiere and P.J. Withers, Acta Mater. (Accepted for Publication May 2000), 2000.
[27] M. Preuss, E. Maire, J.-Y. Buffiere and P.J. Withers, submitted to Acta Mater. (June), 2000.
[28] "Sirius Science", CCLRC report 1998, Ed. W. Gelletly.
[29] M. Preuss, E. Maire, J.-Y. Buffiere and P.J. Withers, submitted to Acta Mater. (June), 2000.
[30] Debus J *et al*, Int J Radiat Oncol Biol Phys (2000) 47(3) 591-596.
[31] Munzenrider JE & Liebsch NJ, Strahlenther Onkol (1999) 175 Suppl. 2 57-63.
[32] Hug E B *et al*, J Neurosurg (1999) 91 432-9.
[33] Rossi CJ, Strahlenther Onkol (1999) 175 Suppl. 2:82-4.