SCIENTIFIC AND MEDICAL EXPLOITATION OF ACCELERATOR SCIENCE

Introduction

This is a proposal for three linked scientific programmes based on the coherent exploitation of accelerator science. The case falls into two parts:

1) A request for an initial investment, within the remit of the North West Science Review Team, of ca. £12M. This will establish:

   a) A world-class Free Electron Laser facility at the Daresbury Laboratory for use by the UK infra-red scientific community (£6M).

   b) A series of linked developments in medical imaging science, drawing together academic and clinical specialists from the Universities of Liverpool and Manchester and the UMIST, the Clatterbridge and Christie Hospitals, the Patterson Medical Institute and the Daresbury Laboratory (£6M).

2) An outline proposal for a flagship project to be based at the Daresbury Laboratory, exploiting the skills of the staff and the infrastructure there so as to enhance the scientific base in the North West and boost the regional and national economy.

The flagship project 2) builds on the proposals in 1) and is appropriate for funding by the North West Science and Daresbury Development Group. It will establish a unique world-leading facility providing beams of radioactive isotopes for fundamental research and create a major upgrade to the clinical and isotope production activities currently undertaken at the Clatterbridge Hospital. It will also establish an innovative, fourth-generation, light source (4GLS) Free Electron Laser complex with world-leading capabilities for research in the biological, physical, nuclear and medical sciences

We appreciate that the substantial investment requested for the flagship project will require a more detailed case than that presented here. In particular it will require two design studies lasting a total of three months in order to resolve essential design parameters of the instruments needed and provide accurate costings. We request £0.5M from the North West Science Review Team for these design studies.

A key feature of this proposal is that it builds on the existing internationally acknowledged expertise in accelerator science that is present in the Daresbury Laboratory and at Lancaster University. When combined with future investment in equipment, this will provide unparalleled opportunities for exploitation in fundamental and applied science and medicine, on the Daresbury site and in the North West universities and hospitals. Further, this expertise provides the basis for UK involvement in future international accelerator-based science projects. The linear collider currently under development by collaborations based in Europe, the USA and Japan is a case in point. UK scientists will not have access to this machine, crucial to developing our understanding of fundamental physics, unless the UK make a substantial contribution to the design and construction of the collider. Indeed, the reputation of the Daresbury accelerator scientists is such, that both the European and American groups have already requested their support in the design of the linear collider.

The proposal is a collaboration between:

- The national Nuclear Physics community, spokesman Prof. John Durell (University of Manchester), and groups from …

- The national infra-red community, spokeswoman Dr Andrea Russell (University of Southampton), and groups from …

- Researchers working in those fields of physics, chemistry and materials science that would benefit from the 4GLS, spokeswoman Prof. Wendy Flavell (UMIST)

- The physics departments of the universities of Liverpool, Manchester, UMIST, Salford, Lancaster.

- Medical/ clinical scientists, spokesman ? …

- Daresbury Laboratory staff, spokesman Prof. David Norman (Daresbury Laboratory).

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

Radioactive Beam Facility for Basic Science Research 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, environmental studies and tests of the Standard Model. The entire UK nuclear physics community enthusiastically backs this proposal. 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 the 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 (>100μA) beam of 200MeV 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 should 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 10MeV/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.

Fundamental Science

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 a range of 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 Interactions. 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.

Nuclear techniques have found widespread use in medicine for both diagnosis and therapy. In many of these applications one uses radionuclides as tracers but in others their decay properties are exploited for imaging or other purposes. To date radioactive tracer applications in vivo have not been fully exploited because of the limited range of tracers available. With the new facility, a large variety of nuclear species suitable for differing applications will become available. By the same token it will supply a wide range of species suitable for PET studies. The same tracer techniques are also ideal for the study of tribology and environmental problems. For example, concerns over the leakage of long-lived fission products in radioactive waste storage can be addressed by implanting short-lived isotopes of the same chemical element, hence speeding up simulations of the processes of interest.

Medical Therapy

The choice of a 200MeV proton cyclotron as the driver accelerator provides another crucial role for the new facility, as a proton radiotherapy centre. There are presently 13 proton therapy facilities world-wide with beam energies in excess of 150MeV. Clatterbridge Centre for Oncology (CCO) is the only group in the UK providing proton therapy, with a maximum energy of 62MeV, sufficient to treat superficial tumours, such as those of the eye. Treatments are provided in collaboration with four specialist ophthalmology centres that provide a national pattern of referrals to CCO. Only three other centres internationally have achieved a greater level of patient experience for this type of work.

Higher energy beams of protons may be used to treat deep-seated tumours, presently treated using photon (X-ray) radiotherapy. However, X-rays can damage critical tissues adjacent to the tumour site, and the technique of Intensity Modulated Radiotherapy (IMRT) has been recently developed to try to overcome these problems. Proton beams have an advantage over photons in that the protons have a finite, energy-dependent, range. This extra degree of freedom, not available with photon therapy, allows the doses to nearby tissue to be minimised. It has long been recognised that proton therapy provides the treatment of choice for certain skull-based or spinal tumours such as Chordoma and Chondrosarcoma, and proton therapy has provided a vehicle for delivery of high-dose boosts to other clinical sites such as the prostate.

Although very promising, proton therapy is a technique in its infancy and much clinical research is needed world-wide before its routine use: this proposal will catapult the North West groups into the forefront of this research. The efficacy of new treatments such as IMRT needs to be assessed by comparison with existing ‘gold standard’ treatments. There is still no clear understanding of the relative merits of modern proton therapy and IMRT for irregularly shaped tumours. The North West is better positioned than other centres to undertake such comparison studies as both Christie Hospital and CCO have conformal therapy and IMRT research programmes in place and have a combined catchment population of about 6 million. CCO provides neuro-oncology services in association with Walton Neuroscience Centre, the largest centre of its type in the UK, and has established stereotactic radiotherapy for brain tumours and metastases and has recently introduced a programme of stereotactic conformal therapy for skull-based tumours. This work is to be extended to non-malignant tumours and functional disorders of the brain, and clinical research in this area would be greatly facilitated by the availability of high-energy proton beams.

The development of high-energy proton therapy will require provision of a treatment gantry plus a significant increase in the clinical support infrastructure. Imaging facilities will be required to ensure accurate positioning, which will fit alongside the proposal for development of Daresbury as a centre for specialist imaging. Ultimate accuracy will necessitate research into treatment gating to avoid organ movement problems, fitting naturally with Daresbury as a centre for specialist electronics and beam control developments. In addition, a therapy programme of the type outlined above will involve development of specialist computing which will fit synergistically with expertise at Daresbury in this area.

The proton therapy beam line will require only a few nanoAmps of current. Such beams can therefore be provided in parallel with nuclear physics requirements. The programme to produce isotopes in support of clinical research and service programmes in the North West can likewise be run in parallel and greatly expanded, as explained previously. In this context, the reduction in distance to the Christie Hospital, which is currently the primary user of short-lived radioisotopes, is an added advantage. Further areas of specialist research may be to develop energy variation of the therapy beam (to provide range modulation) whilst maintaining constant energy for parallel research projects. For these areas, the specialist expertise of the Daresbury accelerator group will be required.

In short, the proposed new facility will permit the scientific community to carry out an exceptional range of research over many scientific disciplines while simultaneously providing a considerably enhanced capability for proton therapy treatment and radioisotope production in the North West. To take advantage of this unique opportunity requires an investment to begin design and construction.

Costing

The total cost of the facility (including £4M contingency) is estimated to be £50M (all figures ex VAT): £17.5M for the driver accelerator and shielding (immediate benefit: proton therapy and source production); £2.5M for the treatment gantry; £10M for high-activity target and low-energy transport line (non-nuclear science programme); £16M for ion source, postaccelerator, control and services (nuclear physics programme). The Nuclear Physics facility will require instrumentation for the science programme. A considerable amount of money has been and is being invested in equipment used by the Nuclear Physics community at overseas laboratories. 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.

Advanced Imaging Centre

Despite the enormous growth of imaging science, there is no UK centre of excellence. We propose to establish such a centre, dedicated to improving all aspects of the subject – image production, detection, storage, analysis, and visualisation – by means of a network to co-ordinate the expertise scattered throughout the North West and take advantage of cross fertilisation between areas such as medical imaging, materials science, detector development for particle physics, life sciences, non-destructive testing and others.

State of the art facilities, especially but not exclusively for medical imaging, will be located in several centres, creating an outstanding multidisciplinary team of sufficient size and stature to make the North West a world leader in advanced medical and industrial imaging.

Imaging technology	
Detector Development	Daresbury, UMIST and Liverpool University
Advanced source instrumentation	Daresbury: synergy with advanced isotope production and 4GLS
Magnetic resonance	Walton Centre for Neurology & Neurosurgery (WCNN), Hope Hospital, Manchester & Liverpool Universities
PET	ManPET, Liverpool
CT	????
X-radiography	North Western Medical Physics (NWMP)
Image engineering	UMIST
Image analysis and visualisation	ISBE-Manchester University, UMIST, Salford, Daresbury
Medical Imaging	
Medical Physics	NWMP, Clatterbridge, Royal Liverpool
Neurology	Hope Hospital, WCNN, Clinical Research Facility
Oncology	Christie, Clatterbridge, Preston
Non-destructive Testing	
Materials science	Manchester University, UMIST
Civil Engineering	Salford University

Despite the apparent diversity of the technologies and applications mentioned above there is considerable overlap between them. In recent times, a consistent pattern has begun to emerge in which the requirements for imaging are increasingly functional instead of purely morphological. In medical imaging there is a clear need to determine the three dimensional distribution of substances such as drugs as a function of time. This requirement is mirrored in the industrial arena where such imaging could play an essential role in improving manufacturing processes or materials performance. Non-destructive testing is of enormous importance because destructive measurements are time consuming and are not easily translated into 3D maps of damaged areas.

The network will have as its primary aim the enhancement of existing and the development of new imaging techniques together with the pursuit of the research that such technologies makes possible. In addition, the network will play a major role in training students and existing professionals. It is envisaged that the combined expertise would feed into existing courses such as the Manchester M.Sc. in imaging. In addition refresher and update courses will be run to keep healthcare professionals and industrialists informed of the current ‘state of the art’.

The key to the success is to tightly link the imaging technology together with the imaging requirements and to facilitate this we wish to create a series of joint appointments between institutions. One example would be joint appointments between Daresbury and the medical schools to ensure that instrumentation developments remain correctly focussed. The imaging requirements reside in two important areas, medical imaging and non-destructive testing for engineering.

On the medical side, several of the partners associated with this proposal have an established imaging network – ManPET, which serves as a model demonstrating the feasibility of such a cross-institution network. This was established for the development and exploitation of medical imaging using Positron Emission Tomography (PET) in the North West. It draws together scientists from a wide range of disciplines (biological scientists, radiochemists, pharmacologists, physicists, image data analysts, bio-mathematical modellers and clinical scientists), to focus on imaging-based research in oncology, neuroscience, and cardiovascular science. ManPET has been successful in establishing a collaborative research programme that is clinically and biologically driven. The addition of the imaging technology partners to this network in conjunction with innovative mathematical techniques, will complete the range of skills necessary to make significant advances in PET science. Such a multi-disciplinary research approach offers a powerful means to provide unique information that cannot be obtained in any other way, and is not available anywhere else in the world.

We have identified that the ultimate aim is to develop rapid three dimensional time resolved molecular imaging at resolutions down to sub micron levels. Since all disease states are associated with changes in cellular and/or tissue biochemistry with consequent effects on tissue structure, the presence and type of disease can be detected by analysing tissue molecular structure. The ability to make time resolved three-dimensional molecular maps in vivo would not only revolutionise disease diagnosis but also the subsequent therapy. Modern therapeutic interventions such as linear accelerator based stereotactic radiosurgery and drug delivery techniques aiming at focal delivery of potent drugs via micro catheters into diseased areas are only possible with the three dimensional identification of the diseased area to target therapeutic efficacy. In addition, advanced imaging is vital to individually monitor the effect of therapy on the disease process and by doing so, detect pitfalls of current therapeutic approaches and design new treatment strategies.

Functional imaging has allowed enormous advances in the understanding and treatment of the epilepsies. In the near future, it may replace invasive electrophysiology to identify foci of epileptic activity in the brain and should revolutionise the current simplified surgical approach of removal of an anatomical area wherein the epileptic activity is located. Since epilepsy is a functional disease, it is foreseeable that a localized modification of neuronal function by either pharmacological or other means is far more appropriate. This will only be possible if the altered function can be localized 3-dimensionally with sufficient accuracy so that treatment can be directed precisely to the focus.

In oncology, the potential of molecular imaging techniques is enormous. Recent data from the Daresbury group clearly demonstrates that significant differences can be detected between, normal breast tissue, benign lesions and malignant tumours using only scattered X-rays. The same work has shown that differences in tissue structure can be detected several cm from a tumour leading to the possibility that such changes may be used to detect tumours that would otherwise be much too small to be detected.

As a start to building up a comprehensive imaging network, we have identified two areas that can make an immediate impact on science and which build upon existing strengths. These are positron emission tomography and advanced X-ray imaging.

Initial facilities

Dedicated imaging beamline on the SRS: the X-ray Imaging "Gold Standard"

Transmission X-ray imaging has a century-old history and the basic technique has changed little in that time. Recent experiments at Daresbury and abroad have demonstrated that novel techniques, exploiting characteristics of the *scattered* radiation, are now set to take X-ray imaging onto a completely new level. We propose to combine synchrotron radiation, radical detector development and advanced statistical signal processing to produce a world-leading investigatory instrument which will provide both very high resolution imaging and tomography, initially a few μm, with a medium term aim of sub- μm resolution at a wide range of energies. This dedicated beamline will be a "gold standard" system for X-ray imaging and will be inherently multi-functional, taking full advantage of directly transmitted, diffracted and secondary photons. It will allow diffraction enhanced imaging (DEI) which exploits X-ray refractive effects and produces images of extraordinary contrast.

Trials involving Daresbury, Manchester Breast Screening Service and the Christie Hospital have demonstrated that, even with transmission imaging, synchrotron X-rays can be used with ~10x reduction in dose over existing clinical techniques. The enhanced contrast and reduced dose means that an immediate programme could be established to investigate the feasibility of the technique for screening young women at high risk of breast cancer, a problem that conventional mammography cannot address.

The detection of coherently scattered X-rays as well as those that are transmitted allows the creation of images that are sensitive to molecular structure. The most exciting potential application will be to differentiate tissue types and detect various pathologies such as malignancy. The full potential of this technique can only be realised with radical detector development. We will strengthen the existing collaborations between Daresbury and UMIST on detector projects by adding the Liverpool silicon detector centre to create the world leading X-ray detector development consortium. We will also work closely with Philips Medical Imaging in Hamburg to develop a coherent scatter computed tomography (CSCT) system for medical use.

The ability to work in the μm spatial regime will open new fields of study in both material and life sciences and will allow the study of many pathologies which are well beyond the scope of medical CT machines. The new instrument will make possible the non-invasive imaging of delicate structures in their native 3D relationships, contrasting with current techniques such as micro-toning which distort specimens and destroy vital information. Examples include genetically induced defects in embryos, full 3D structures of insect neural systems, the internal structures and communication systems of cells. Of immense importance will be the addition of CSCT and fluorescence techniques, which will allow elemental and molecular maps to be produced. One example is the study of the trabecular structure and mineral distribution in bone, a major interest within Manchester medical school due to its importance in osteoporosis.

For engineering applications, similar advances will be possible with the new instrument. For example, polymer composites are now being introduced into the wing set of Airbus aircraft yet very little is known about the cumulative effects of impact damage due to the lack of adequate testing techniques. Using micro-CT we will be able to visualise the damage non-destructively, thus facilitating the monitoring of the evolution of impact damage during fatigue cycling or after successive impacts. Moreover, it will also be possible to combine tomographic imaging with strain measurement, the potential of which has already been proven by the proposers. Tomographic slices of damaged regions individual SiC fibres within a Ti matrix were imaged and correlated with the level of strain in that fibre and the resulting stress concentration caused by the damage event. This technique has great potential for identifying critical regions in components and assemblies and then evaluation of the local stress level. In a recent round robin comparative study, tomography was identified as the best method of monitoring the densification of powder compacts and sintered products. However, it was found that the procurement of tomography facilities was outside the financial capabilities of the SMEs involved in the study. The availability of an expertly staffed central facility would circumvent this problem giving competitive advantage to UK companies, especially those in the North West. The new instrument at Daresbury will complement the capabilities of the Unit for Stress and Damage Characterisation (USDC) facility in Manchester and it is envisaged that staff will be seconded from one to the other. This will establish the North West as a focus for UK engineering X-ray imaging.

PET Programme

Leading-edge medical imaging research is pivotal to this proposal. Positron Emission Tomography (PET) functional imaging allows the study of 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. For multi-disciplinary PET research to be conducted at a world-class level, state-of-the-art facilities in all areas are necessary.

PET imaging systems for both patient and animal studies are operational on the Christie/Paterson site, using radioisotopes produced using the cyclotron at the Clatterbridge Centre for Oncology, and new radiochemistry laboratories at the Paterson Institute for Cancer Research. The lack of a cyclotron on the Christie/Paterson site is a serious disadvantage for work utilising short-lived isotopes and so it is proposed to purchase a commercial cyclotron as part of this proposal.

The scope and depth of functional imaging research will be substantially enhanced through the establishment of radioisotope production based on the radioactive beam facility proposed for the Daresbury site. In conjunction with the small animal pet camera described below this would create a truly world class PET research facility.

Small Animal PET Camera

The sensitivity of current small animal PET cameras is poor (< 1%) and constrained by the trade-off between the camera sensitivity and the image quality. In-vivo characterisation of new radioligands and radiotracers is vital to move the field forward and demands PET scanners, which are more powerful than current systems.

We propose to build a PET camera with a complete coverage of gamma ray emission angles using a cylindrical geometry with de-mountable end caps. The detectors will be fabricated from germanium having 2D position sensitivity. There will be two concentric layers of these detectors, the outer layer having a high stopping power for the gamma rays. Using this configuration as a Compton camera, the direction and energy of the incoming gamma ray can be determined, as well as its position. This will allow the accurate use of events in which one or other of the gamma rays have been scattered to large angles. A far greater proportion of the total emission can therefore be included in the image reconstruction, improving the sensitivity by at least 10 times. The projected count rates from the camera of 108 per second will require the design of fast asynchronous event processing, for which the Daresbury Laboratory instrumentation group is internationally renowned. The detector modules will be provided by our industrial partners, Perkin-Elmer, from a novel design made in collaboration with them.

The synergy between the development of the radiochemicals, state of the art detector and system design, and advanced imaging technology will be a strong feature of the partnership between Daresbury and the North West medical imaging community. The establishment of the above mentioned facilities as a resource for medical imaging research will strengthen the science base in the region, and establish the North West as a world centre of excellence in functional imaging research.

Medical Technology Group

The creation of a dedicated group of 5-6 high quality instrumentation scientists and engineers at Daresbury with the specific remit of developing medical instrumentation would be a major step forward in linking clinical with basic science and instrumentation. Such a group would be unique in having access to the advanced physics engineering facilities on the Daresbury site, whilst also being tied into a North Western clinical network. The group would be responsible for the development of advanced X-ray imaging techniques utilising the dedicated imaging beamline and also for the development of the small animal PET scanner.

Initial costing

For the first stage of the Advanced Imaging Centre, which is ready to start now, we seek funding of £6M from the North West Science Review Team. The later developments, appropriate for financial support from the North West Science and Daresbury Development Group, will require further funds of £8M?.

The bid to the North West Science Review Team comprises £2M for the imaging beamline on the SRS; £1M for the small animal PET scanner; £1.5M for the cyclotron at Christie Hospital; £1M for an upgrade to radiochemistry facilities at the Patterson Institute and £0.5M for new imaging facilities at ManPET.

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 region; 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 millimetre to visible and potentially the ultraviolet to 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 facility via an EPSRC funded project. However, this project will end in the next 18 months and may then be renewed annually. The access to FELIX is insufficient to satisfy the projected UK user community. Locating a new IR-FEL at Daresbury Laboratory will provide UK scientists with a flexible radiation source in an environment which will enable new interactions with other advanced light sources (the SRS and other parts of 4GLS) opening up unexplored fields of enquiry.

The 4GLS facility will contain three free electron lasers:

- An **IR-FEL** to generate radiation in the range 5μm to 1mm (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 electron laser radiation is here now *but* it is demanding. Making electron lasers work in the IR and VUV regions is already proven. In the XUV, the Tesla Test Facility FEL has shown that electron laser 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. **We request funding from the North West Science Review Team to build the IR-FEL facility now.**

IR-FEL

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 100 μm. 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:

Parameter	FELIX	Stanford	Daresbury
Wavelength range	5 to 100 μm	μm	μm
Macropulse repetition rate / Hz	5	20	50
Macropulse duration	4 μs		μs
Micropulse repetition frequency	1 GHz	11.818 MHz	1 GHz
Micropulse width	ps	ps	ps

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

- The unique interaction with the other components of 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 the IR-FEL at the 4GLS

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! If the two sources have short pulses then 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. Such amplifiers have yet to be studied in depth due to lack of suitable combinations of optical/IR sources. 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. In the biomedical sciences the effects of protein folding and single residue mutations on the vibrational energy transfer and dissipation within biological systems may be investigated, and the synergy with the BBSRC structural biology centre at Daresbury will be important. Applications are likely to include photosynthesis and investigating the harmful effects of different wavelengths of sunlight on plants and animals. The non-bonding, environmental interactions which exist in condensed phase systems may also affect vibrational lifetimes, e.g. pump-probe measurements may be a sensitive probe of ligand-protein interactions in the binding pocket of metallo-proteins and enzymes.

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 ~6μs for a 27mm^2 active area are possible. This collaboration could lead to a spinout company (see letter of support), 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 (~5μm). Traditional scanning tip methods have limited data collection rates to ~1 minute per image, but the "tipless near-field spectroscopy" technique has overcome this and data acquisition rates of 40ms 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.

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.

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 imobilising 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, building 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. FEL light offers the exciting prospect of imaging tissue to a resolution of a few µm. This technique relies on the short pulse structure of the FEL, as the ballistic photons pass straight through tissue. Diffusive or Rayleigh scattering of light through tissue has traditionally hindered the development of optical based techniques in most biomedical applications. At conventional laser wavelengths the Rayleigh scattering dominates, blurring and distorting the image. However, as Rayleigh scattering varies with λ^{-4}, use of the wavelengths provided by the IR-FEL elegantly overcomes this problem to provide sharper images at greater depths within the sample.

Ablation and Surface Modification. The high peak power, tunability, and pulse structure of the FEL output enable its use in the modification of surfaces by ablation 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 hydroxyapatitie, 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. 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. FEL output has also been shown to be useful in repairing corneal tissue and in wound healing. The multi-user nature of the IR-FEL facility would make treating patients a realistic prospect. The IR-FEL could also provide a standard to match the optimal choice of conventional lasers for specific tissues in ablation therapy.

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 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. In the USA a consortium 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. 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.

VUV-Free Electron Lasers

The VUV-FELs will have particular impact upon the biological, physical and medical sciences. They are crucial components of the pump-probe, two-colour, experiments already described and also enable many new techniques.

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 150nm and 230nm 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** will for the first time allow us to distinguish the role of chromophores of amino acid side chains in folding. 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.

Microscopy. The inclusion of **confocal microscopy** will allow time-resolved structural studies on organelles and sub-cellular structures in cell and tissue cultures at spatial resolutions <100nm. This is important to the pharmaceutical industry and to the development of connections between organic and semiconductor systems. The development of **evanescent wave microscopy** has the potential to study single molecules on the surface of the cell in real time.

The Physical Sciences. The spatial and timing properties of 4GLS in the VUV region will open new possibilities in imaging and dynamics studies of materials. The high intensity, tunability and polarisation will facilitate novel resonant measurements, time-resolved spin measurements and sum/difference frequency experiments on a range of materials (*e.g.* novel magnetic architectures and chiral systems). The coherence of the VUV radiation will permit experiments with unprecedented resolution to be carried out. 4GLS combined with the radioactive beams facility will also enable novel fundamental research in the physical sciences.

Nanoscale Materials. The feature size on semiconductor chips has reduced logarithmically for three decades. Future developments require control of the terminal characteristics on a nanometre scale and ultra fast studies of carrier dynamics. The output from 4GLS offers unparalleled opportunities in the study and development of nanoscale materials of all types.

Nanocluster Research. Up to now synchrotron radiation has been used to measure the electronic and magnetic properties of exposed clusters in the size range 1 - 5 nm supported on surfaces in UHV and also particles embedded in matrices. These particles mark the boundary between molecular and solid state systems and have properties distinct from both. They offer the possibility of exciting technological applications. A VUV-FEL will realise the goal of **wide band VUV and XUV photoemission measurements on free clusters**.

Molecular Reaction Dynamics. 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 VUV laser used to ionise the molecule and the fragments identified using the IR laser. These studies address issues that are fundamental to molecular structure, a necessary prequisite for understanding intermolecular reactions.

Coherence. The 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, 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. 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 VUV-FEL and will shed new light on the behaviour of free and loosely bound electrons in the presence of high intensity radiation. The coherent excitation of atomic or molecular ensembles will yield a unique probe of plasma properties, giving the possibility of developing novel laser mechanisms in the VUV.

High Resolution Studies of Materials/ Dilute Systems. Electron lasers will revitalise the field of photoemission by enabling the electronic structure of materials to be probed with unprecedented angular and energy resolution and at ultra-dilute concentrations. Studies around the Fermi surface are crucial for understanding superconductors and transport properties.

Magnetic Phenomena. Spin electronics is a new and rapidly developing field with the potential to supplant silicon technology. However, the realisation of this potential will require the increased photon flux of a VUV-FEL to enable high-resolution studies of the spin-dependent electronic structure of materials. Magnetic materials characterisation by optical methods is complementary to the photoemission methods described above and the 4GLS lasers 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 (NOMOKE). These techniques are particularly attractive for the study of industrially relevant thin films and interfaces. The continuous tunability and high intensity from the VUV-FEL will also enable both sum/difference frequency experiments and resonant measurements.

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.

Approximate Costs

The total cost of the 4GLS facility is likely to be around £60-70M. The IR-FEL is ready to start construction now, and we seek funding now from the North West Science Review Team of £8M to build the IR-FEL facility, including 100 MeV linac and 4 end stations. We also seek immediate funding of £0.25M for a three-month design study to hone the proposal and produce firm costings that will be put forward to the North West Science and Daresbury Development Group.

For guidance purposes only, the current thinking for the 4GLS envisages 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 rough cost estimate for the facility comprises £2M for a 300 MeV linac for SASE VUV FEL; £1.5M for the 'SASE' XUV-FEL; £2M for a 300 MeV linac for further acceleration prior to injection into a storage ring; £25M for a 600 MeV storage ring to house the VUV-FEL; £2M for the VUV Cavity based FEL; £10M for 4 undulator beam lines; and £15M for building costs. We emphasise that the detailed design needs work and that these figures are rough budgetary estimates only.

Buzz-word checklist!:

Meets the key criteria of

Quality of science

Impact on the North West science base

Impact on the future of the North West economy

‘Proposal attributes’

Critical mass

Additionality

Add value in the long term

World-class science

Feasibility

Unique opportunity

Good fit

Creative

Interdisciplinary

Knowledge transfer

Out-of-the-box

Enabling strengths and skills

Youth

Collaboration across the region

People, equipment and buildings

Core people

Out-reach

Small number of critical elements

Training for the future

Synergistic bids with substantial overlap

Eventual need for £100-200M

Exciting future for multidisciplinary North West science and secure the future of Daresbury Laboratory

Partnership of all the major academically-based North West institutions

Including new partnerships, cutting across existing structures and not previously envisaged (‘out-of-the-box’)

Fit the Regional Strategy

North West Development Agency

Partners:

- Universities of Liverpool, Manchester, UMIST, Lancaster and Salford
- Medical schools at Liverpool and Manchester
- Hospitals at Clatterbridge, Paterson and Christie
- Companies … inward investment … several companies have already indicated their interest in moving to the North West or in establishing extra R&D or manufacturing facilities alongside the Daresbury accelerator centre.
- Daresbury Laboratory

Underlying theme is based on accelerators

Detectors

Advanced instrumentation

And, above all, people

Funding bid and spend profile

Management plan and milestones

Appendix … list of collaborators and institutions? … supporting letters from industry …