Institution: Keele University

Unit of Assessment: B9 Physics

Title of case study: The development, support and exploitation of Synchrotron radiation and Neutron scattering facilities

1. Summary of the impact

Keele University has made sustained and seminal contributions to the development and use of central facilities (Synchrotron radiation, Neutron scattering) which started over 30 years ago and are still in progress today. Past and present academics at all levels from Keele who began this work have gone on not only to carry out their own ground breaking research using these facilities but, in many cases, to have a major social, economic and industrial impact, through key roles in development, support and techniques and through the present, current and next generation of scientific, management and technical expertise at Central Facilities around the world. This includes numerous postgraduate students, Research Associates and academic staff. The contribution to Science and Technology has enabled significant breakthroughs in many aspects of science and medicine, accompanied by direct economic and social impact and a unique and ongoing contribution to the current generation of SR and neutron sources, their scientific staff and their users.

2. Underpinning research

This case study is based on the seminal contribution made by Keele University staff to the ongoing development, support, management, use and world-wide exploitation of Central Facilities. The impact was and continues to be enormous for those who exploit Central Facilities for scientific, technical and commercially motivated research across the physical and life sciences. Over thirty years ago in the then Department of Physics at Keele, Watson **Fuller** and John **Helliwell** (who went on to play a pivotal role in not only methods development but also management and Leadership, for example as CCLRC Director of SR Science based at Daresbury (2002); President of the European Crystallographic Association (2006-2009); Editor in Chief Acta Crystallographica (1996-2005)) were central to the development of the dedicated Synchrotron Radiation Source (SRS) at Daresbury for protein crystallography, fibre diffraction and small angle scattering for the investigation of molecular structure and organization in a wide range of naturally occurring and synthetic materials. Later developments included Magnetic Scattering led by Keele Professor Bill **Stirling** (1987-1995) who went on to be Director General of the ESRF (1999-2008), and Andy **Fitch** (Keele Staff 1986-1998) who was central to the development of powder diffraction facilities at the SRS and now leads at the ESRF through beam line ID31. Early names at the PG/RA level include Trevor **Greenhough**, who went on to spend many years as a central figure in the development of Protein crystallography facilities and applications at Daresbury (1986-1997), including Lead of the EPSRC supported UK 7.2 CRG (1994-1997), Ian **Glover** (1990 – 1998) who led the development of station 9.5 and anomalous dispersion and diffuse scattering applications at Daresbury, and Trevor **Forsyth** who played a similar role in SR Fibre diffraction (1989-1998) and has gone on to make further major and continuing contributions in neutron scattering at the ILL, Grenoble (1998 – current).

Keele Postgraduate students whose input continues to impact internationally include Dean **Myles** (PhD awarded 1992) initially PDRA at Keele (1989-1996) with particular responsibility for station 7.2; then Staff Scientist EMBL Grenoble and Station Scientist ILL Grenoble and currently Director, Neutron Scattering Sciences Division at Oak Ridge National Laboratory USA), Annette **Shrive** (PhD awarded 1991) who played a key role in developing the SR Laue technique (1988-1999) and is now on the academic staff at Keele (1999 - current), Paul **Langan** (PhD awarded 1990), initially beamline scientist at ILL (1994-1998) and now Team Leader of the Proteomics and Neutron Protein Crystallography team at Los Alamos Neutron Scattering Centre (1998-current), Marisa **Martin-Fernandez** (PhD awarded 1993) leader of the Functional Biosystems Imaging group at Diamond (2008-current), and A. **Gonzales-Alvarez** (PhD awarded 1993), senior staff scientist at Stanford SR Light source. Chris **Martin** (PhD in Biophysics, Keele 2001) became Senior Staff Scientist at the SRS supporting the XRD and NCD user communities.

Myles (1989-1996), **Shrive** (1991-1995) and **Langan** (1990-1994) also worked as Postdoctoral fellows variously at Keele, Daresbury and RAL, developing techniques and supporting users, while the PDRA Sue **Bailey** went on to coordinate and lead the world-leading CCP4 as a Higher Scientific Officer at Daresbury Laboratory (1993-2001). James **Nicholson** (Keele RA on the **Greenhough** 7.2

CRG EPSRC redevelopment grant 1994-97; staff scientist at the SRS to 2008) is now based at Diamond as a Senior Beamline Scientist (2010-current). Joanna **Collingwood** (Keele PDRA and RCUK Academic Fellow, 2003-2009) with Jon **Dobson** (2000-current), made key contributions to the development and application of high resolution x-ray absorption spectroscopy techniques at central facilities (Argonne National Laboratory Advanced Photon Source; Diamond), and currently serves as a member of the STFC Science in Society panel, and has chaired the Diamond Light Source User Committee since its formation in 2009. Current Keele staff continuing the theme of facility and methods development and support include Trevor **Forsyth** (now on secondment to ILL/EMBL and leading a team of ILL and Keele staff as head of the ILL/EMBL deuteration Laboratory), Josep **Sule-Suso** (SR FTIR spectroscopy; Chairman 2007-2013 of the B22 MIRIAM infrared beamline working group at Diamond, and member of Peer Review Committee 5 "Biology-Health" of the Soleil synchrotron, France) and Neil **Telling** (SRS 2002-2008, developing techniques and facilities in Magnetic Spectroscopy and using SR spectroscopy and scattering techniques to probe magnetic materials) whose current work centres on applications of SR to the study of nanoparticles.

3. References to the research (indicative maximum of six references)

1. **Shrive, A.K**., Cheetham, G.M., **Holden, D.**, **Myles, D.A.A**., Turnell, W., Volanakis, J.E., Pepys, M.B., Bloomer, A.C. & **Greenhough, T.J**. (1996) Three Dimensional Structure of human C-reactive protein. *Nature Structural Biology,* 3, No. 4, pp346-354.
2. **Fuller, W., Forsyth, V.T. and Mahendrasingam, A**. (2004) Water-DNA interactions as studied by X-ray and neutron fibre diffraction. *Philosophical Transactions of The Royal Society B Biological Sciences*, 359, No. 1448, pp1237-1248
3. **Fuller, W.**, Blundell, D.J., Eeckhaut, G. and **Mahendrasingam, A**. (2005) Time-Resolved SAXS/Stress-Strain Studies of Thermoplastic Polyurethanes During Mechanical Cycling at Large Strains. *Journal of Macromolecular Science*, Part B, 43, No. 1, pp125-142.
4. Dumas, P., Sockalingum, G.F. and **Sulé-Suso, J.** (2007). Adding synchrotron radiation to infrared microspectroscopy: what's new in biomedical applications? *Trends Biotechnology* 25, pp40-44.
5. Coker, V.S., Gault, A.G., Pearce, C.I., van der Laan, G., **Telling, N.D**., Charnock, J.M., Polya, D.A. & Lloyd, J.R. (2006). XAS and XMCD evidence for species-dependent partitioning of arsenic during microbial reduction of ferrihydrite to magnetite. *Environ. Sci. & Tech*. 40, 7745-7750.
6. New sources and instrumentation for neutrons in biology, **S.C.M. Teixeira**, **V.T. Forsyth**, **P. Langan**, **D.A.A. Myles** *et al. Chem. Phys*.(2008) 345, 133-151.
7. Vellieux, F.M.D., Hajdu, J., Verlinde, C.L.M.J., Groendijk, H., Read, R.J., **Greenhough, T.J.**, Campbell, J.W., Kalk, K.H., Littlechild, J.A., Watson, H.C. & Hol, W.G.J. (1993) Structure Determination of Form I glycosomal GAPDH from *Trypanosoma brucei* using the Laue Method. *Proceedings of the National Academy of Sciences*, 90, pp2355-2359.

Grants showing the role of Keele staff in developing, supporting and running Central facilities

Station 7.2: a new Development in the Application of SR to Structural Molecular Biology
T.J. Greenhough; £249,291 from SERC 1/2/94-31/3/97.

The development and support of Station 7.2 at the SRS, Daresbury
T.J. Greenhough; £60,000 from Research Councils Joint Biology Programme (Joint Appointment) 1/10/94-30/9/97.

Development and Applications of Laue Diffraction in Virus Crystallography
T.J. Greenhough and M.G. Rossmann (Purdue); £60,998 + 100 SRS shifts; SERC 1/10/91 - 28/2/95.

The development and support of Laue diffraction at Daresbury Laboratory.
T.J. Greenhough £60,000 (£20,000 pa) from SERC and MRC (Joint Appointment). 1/10/91-30/9/94.

The development of neutron diffraction at the ILL for the study of biological and industrial polymers
PI V.T. Forsyth; £148,350 (2012) from ILL; £357,701 (2008) from ILL; £282,806 (2003) from ILL

Deuteration initiative for neutron scattering and NMR studies of biological molecules
V.T. Forsyth; £691,468 from EPSRC (2006-2009) (with S. Teixeira, W. Fuller); £289,354 from ILL (2010); £800,878 from EPSRC (2003-2006) PI W. Fuller

Beamline D19: A fast monochromatic diffractometer for single crystal and fibre diffraction

studies in chemistry, physics and the biosciences.
V.T. Forsyth with J.A.K. Howard (PI) , M. Davidson, W. Fuller, S.A. Mason; £1,068,974 from the EPSRC (2002-2006)

4. Details of the impact (indicative maximum 750 words)

As clearly and specifically described in the comprehensive STFC 2008 publication ***The Social & Economic Impact of the Daresbury SRS*****,** the impact of central facilities has not been restricted to the science itself. This publication states that "Impacts from the SRS include the creation of knowledge, improved quality of life in the UK, the generation and transfer of skills, improved competitiveness of industry, the commercialisation of technology, financial effects and the creation of jobs." The input of many Keele staff to central facilities, particularly the SRS and the ILL, has been in instrumentation, techniques, support, and training, each of which impacts significantly at many economic and social levels. This publication also highlights the impact of Joint appointments as an important aspect of the skills exchange between the SRS and host Universities and in bringing. science drivers and challenges to the SRS from the Universities. Keele University was central to this exchange, providing a series of academics as joint appointments (including **Greenhough, Glover, Greenall, Stirling, Catlow, Fitch**) from the first days in 1981 through to closure of the SRS in 2008.

The 2007 ***Research Councils UK report by PA*** consulting, "***Study on the economic impact of the Research Councils***" has a section specifically devoted to the impact of Protein Crystallography (PX) at the SRS, where Keele led from day 1 through several Joint appointments and subsequently Keele PhD students who moved to positions there and elsewhere following graduation. "At the heart of Central Facilities are the development scientists and the user support staff, forming a focus for serving and training a vast community of engineers, scientists, academics and pharmaceutical companies." The report details examples of the contribution of PX at the SRS to drug discovery, citing the enzyme purine nucleoside phosphorylase (teams from Alabama and Keele including **Greenhough**) which provided a starting point to design new drugs to target diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis and Crohn's disease, one of which underwent clinical trial and was licensed to a major pharmaceutical company. The report adds that commercial users of the PX facilities included 16 pharmaceutical and biotechnology companies such as AstraZeneca, GlaxoSmithKline, Pfizer and Astex Therapeutics.

The impact that Keele continues to have through Central Facilities and current (**Forsyth, Teixeira, Greenhough, Sule-Suso, Telling**) past (for example **Myles, Langan**) and future Keele researchers (currently 12 Keele PhD students are engaged in projects utilising Diamond, ILL, the ESRF, APS, SOLEIL) is huge. The ***RCUK report by PA*** confirms this by showing that "Structural biology and the way it is done now would not be possible without the SRS and the subsequent development of other sources. Difficult proteins would not have been solved without the improvements in technology and the speed of crystallographic structure determination would be prohibitive." This applies to the human C-reactive protein structure, a landmark work in 1996 led by two still current Keele staff (**Shrive**, **Greenhough**) and made possible by the SRS following some 50 years of effort world wide. Cited 190 times, it continues to underline the impact of basic science on medical practice, underpinned by widespread publicity ranging from blanket GP circulars (print and video) to Newsweek. This raised awareness, and the scientific work itself, has contributed significantly to the subsequent debate surrounding the molecule and its role in CVD and to the increased importance of raised levels in the clinical setting, particularly for at-risk patients. The ***RCUK report by PA*** also confirms that "the ribosome structure, a fundamental scientific breakthrough which may lend itself to drug discovery, relied heavily on the ability to rapidly screen crystals at the SRS". This screening was carried out on stations developed and supported by Keele staff.

While closure of the SRS in 2008 ended almost 30 years of pivotal Keele involvement in the support, training and achievements of many thousands of Daresbury users, with lasting impact on the "scientific, industrial and skill base of the UK", the Keele impact then accelerated through leading roles in the establishment of the next generation of central facilities with many continuing to play key roles in training, advising and transferring key skills and technology to these facilities. The subsequent and current senior roles at these new facilities continue to impact on a global scale.

Keele has played, and continues to play through **Forsyth** and **Teixeira**, a major role in the development, support and exploitation of neutron scattering for the study of biological molecules and

industrial materials, impacting particularly on the pharmaceutical and polymer industries and the training of the next generation of scientists with diverse and essential skills for the workplace. The 2012 STFC report on Neutron scattering ***Materials research for modern life*** (STFC, 2012) gives examples of the significant medical, social and economic impact that neutron scattering science contributes to our lives, with the study of biological molecules enabling "Multidisciplinary teams of medics, physicists, materials scientists, chemists and engineers to come together to make key breakthroughs in using materials in medicine". Much of this work has been made possible through the input and expertise of Keele staff. Major awards of over £2m to **Forsyth** and **Fuller** with a variety of collaborators provided the funding to develop the facilities and construct "A Laboratory to support the Deuteration of Biological Macromolecules" (Led by **Forsyth** in collaboration with **Myles**, then at EMBL) as outlined in the ***ILL Millenium Programme proposal of 2001***. In January 2003, ***Business,*** the quarterly magazine of the BBSRC, included reference to the major Keele-led developments in progress at the ILL which will "mean that biologists can contemplate experiments that were simply impossible previously", while the ***EPSRC Newsline*** reported that a key aim of the facility was to "develop and train the UK user base" for these techniques.

In 2013 the ***Report from the ILL Associates' Working Group on Neutrons in Europe for 2025*** concluded that neutrons will remain an essential tool for science and industry including not only materials science but also the environment, life sciences and information technology. "Some two thirds of neutron scattering studies contribute directly to or closely underpin the needs of industry". Keele, through **Forsyth** and **Teixeira**, and the next generation of Central Facility experts currently being trained as PhD students between Keele and the ILL, will continue to play a pivotal role in delivering and exploiting this science and enabling the accompanying economic and social impact.

5. Sources to corroborate the impact (indicative maximum of 10 references)

- **New Light on Science: The Social & Economic Impact of the Daresbury Synchrotron Radiation Source, (1981 – 2008) (**STFC 2008)
http://www.stfc.ac.uk/resources/PDF/SRSImpact.pdf

- **Study on the economic impact of the Research Councils** (RCUK 2007)
The 2007 Research Councils UK report by PA consulting,
http://www.rcuk.ac.uk/documents/keireports/EconomicImpactResearchCouncilsPart2CaseStudies.pdf

- **Neutron scattering: Materials research for modern life** (STFC, 2012)
This brochure gives examples of the significant social and economic impact that neutron scattering science contributes to our lives.
http://www.stfc.ac.uk/resources/PDF/Neutron_Scattering_brochure_FINAL.pdf

- "**Business**" Quarterly magazine of the Biotechnology and Biological Sciences Research Council January 2003. Available at http://www.ill.eu/sites/deuteration/EPSRCpage.htm (BBSRC 2003)
http://www.ill.eu/sites/deuteration/EPSRC_Files/january_03_bbsrc_article.pdf

- **EPSRC Newsline** http://www.ill.eu/sites/deuteration/EPSRC_Files/Newsline24_article.pdf
available at http://www.ill.eu/sites/deuteration/EPSRCpage.htm

- **The ILL Millennium Programme 2001:** A Laboratory to support the Deuteration of Biological Macromolecules (ILL 2001)
http://www.ill.eu/about/future-planning/the-millennium-programme/millennium-symposium-2001/

- **Report from the ILL Associates' Working Group on Neutrons in Europe for 2025** (ILL 2013)
http://www.ill.eu/fileadmin/users_files/documents/news_and_events/news/Report_from_ILL_Neutron_Working_Group.pdf

- Consultant, Diamond Life Sciences; former head of Protein Crystallography at the Daresbury SRS

- Professor of Molecular Biophysics, LMB Cambridge and BCA President 2009-2013

- Director, Life Sciences Diamond, MRC Professor of Structural Biology at the University of Oxford and Head of Structural Biology, Wellcome Trust Centre for Human Genetics

- Chair, BBSRC Council and Director of Research, Department of Biochemistry, University of Cambridge