Institution: Newcastle University

Unit of Assessment: 8 Chemistry

Title of case study: International synchrotron facilities for crystal structure determination

1. Summary of the impact

This case study describes impact from the Newcastle-led research project to construct the world's first dedicated single-crystal diffraction synchrotron beamline for chemistry and materials science at Daresbury Laboratory Synchrotron Radiation Source (SRS). The result was an innovative and productive facility that has served as the model for the development of other facilities internationally, especially at Diamond Light Source (UK) and the Advanced Light Source (USA). The original Newcastle University research has helped produce scientists now employed by industry and public service sectors around the world. Major new and beneficial drugs and catalysts have been developed with the aid of the synchrotron beamlines and work conducted at these facilities has been critically important for the advancement of the global chemical and pharmaceutical industries and US Government energy development programmes.

2. Underpinning research

Crystal structure determination is crucial to our understanding of the properties of materials and is of fundamental importance in physical and life sciences. The technique faces ever-increasing demands for the study of more complex molecular systems. The years 1994–1997 were the main period of a major Newcastle-led research project to design, construct and commission a single-crystal diffraction beamline (Station 9.8) at the SRS, recognising the need for a facility that could greatly extend the range of materials not otherwise amenable to conventional laboratory equipment. Before Station 9.8 was built there were no dedicated facilities available for the study of crystals with one or more dimensions on the micron scale or other very weak scatterers, as laboratory facilities were not sufficient, and so many important structural insights were lost.

The project team, led by Clegg, designed and set up Station 9.8 using a modified laboratory diffractometer and detector system with X-ray optical components in a novel combination to ensure that the equipment would function successfully with the synchrotron source and also to combat constraints of the available space. Other challenges overcome were the needs for appropriate control and processing procedures and software, and requirements for handling a wide range of samples, including air-sensitive materials, to ensure maximum applicability [P1]. A primary objective was to offer a familiar setup to a non-specialist first-time synchrotron user.

Overall project leadership and direction was maintained throughout by Clegg, on site half-time at Daresbury from 1995 to 1998 through formal Joint Appointments financed as research grants to Newcastle University to cover 50% of salary costs; he was responsible for key decisions regarding the choice of equipment, software and postdoctoral staffing as well as conducting the extensive commissioning work using samples provided by chemists from around the UK and abroad. Station 9.8 was the first dedicated facility of its kind anywhere in the world [P2] and has enjoyed immense success and productivity from the first commissioning data measurement. In 1997, in accordance with the original plan and EPSRC grant conditions, it was formally handed over by Newcastle University as a full SRS user facility, on schedule, within budget, and with performance exceeding the design specifications. It quickly became one of the most heavily oversubscribed beamlines at Daresbury, with academic and commercial users, generating between 10 and 20% of SRS-based publications in subsequent years [P3, P4, P5 & P6].

Continued use of the facility beyond 1997, and of its direct successor at Diamond Light Source after 2008, by Clegg's Newcastle research group included the establishment of a synchrotron-based component of the EPSRC National Crystallography Service (NCS) in 2001, which further raised the profile of the beamline and introduced its benefits to a wide range of UK chemists, some of whom subsequently became commercial users, while others were carrying out research projects with industrial partners; this attraction of a large user community contributed hugely to the success of the proposal to construct Diamond beamline I19.

3. References to the research

[P1] Cernik, R. J., Clegg, W., Catlow, C. R. A., Bushnell-Wye, G., Flaherty, J. V., Greaves, G. N., Burrows, I., Taylor, D.J., Teat, S.J., & Hamichi, M. (1997). A new high-flux chemical and materials crystallography station at the SRS Daresbury. 1. Design, construction and test results. *J. Synchrotron Rad.* 4, 279–286. Corrigendum *J. Synchrotron Rad.* (2000), 7, 40. *The principal technical description of the SRS facility.* 190 citations. [* Key reference]

[P2] Clegg, W. (2000). Synchrotron chemical crystallography. *J. Chem. Soc. Dalton Trans.* 3223–3232. *Describes the context of the research, with specific references to the use of the SRS facility.* 46 citations.

[P3] Camblor, M. A., Díaz-Cabañas, M. J., Perez-Pariente, J., Teat, S. J., Clegg, W., Shannon, I. J., Lightfoot, P., Wright, P. A. & Morris, R. E. (1998). SSZ-23: an odd zeolite with pore openings of seven and nine tetrahedral atoms. *Angew. Chem. Int. Ed. Engl.* 37, 2122–2126. *Early publication of results from the initial project & an example of work that has led to commercial impact.* 68 citations. [***** Key reference]

[P4] Li, X.-C., Sirringhaus, H., Garnier, F., Holmes, A. B., Moratti, S. C., Feeder, N., Clegg, W., Teat, S. J. & Friend, R. H. (1998). A highly π-stacked organic semiconductor for thin film transistors based on fused thiophenes. *J. Am. Chem. Soc.* 120, 2206–2207. *Early publication of results from the initial project.* 320 citations. [* Key reference]

[P5] Hamilton, D. G., Sanders, J. K. M., Davies, J. E., Clegg, W., & Teat, S. J. (1997). Neutral [2] catenanes from oxidative coupling of π-stacked components. *Chem. Commun.* 897–898. *Early publication of results from the initial project.* 76 citations.

[P6] Francis, R.J., Drewitt, M. J., Halasyamani, P. S., Ranganathachar, C., O'Hare, D., Clegg, W. & Teat, S. J. (1998). Organically templated layered uranium(VI) phosphates: hydrothermal syntheses and structures of $[NHEt_3][(UO_2)_2(PO_4)(HPO_4)]$ and $[NPr_4][(UO_2)_3(PO_4)(HPO_4)_2]$. *Chem. Commun.* 279–280. *Early publication of results from the initial project*. 52 citations.

Key grants awarded to Newcastle University:

W. Clegg (PI), C. R. A. Catlow (CI; Royal Institution). A high-flux synchrotron station for single-crystal diffraction. EPSRC. 1994–1997. £1,283,069.

W. Clegg. CLRC Joint Appointment. CCLRC. 1995–1998. £68,500.

W. Clegg. National X-ray Crystallography Service: a synchrotron component. EPSRC. 2001–2006. £527,964.

W. Clegg. Joint Appointment at Daresbury Laboratory. CCLRC. 2001–2007. £84,467.

W. Clegg. National Crystallography Service 2006 renewal. EPSRC. 2006–2010. £345,239.

Quality assurance:

All the EPSRC grant final reports were recognised as Outstanding and Internationally Leading; the NCS synchrotron component was singled out by reviewers for special commendation.

4. Details of the impact

Station 9.8, with its unique design developed by Newcastle University researchers, was the first dedicated facility of its kind in the world. Its rapid and large oversubscription prompted the decision by SRS to establish a second similar station by reallocation of an underused powder diffraction beamline (16.2) a few years later. Both facilities operated until mid-2008 and provided the model, inspiration and (through high demand from users) justification for current facilities in the UK and worldwide. Impact from commercial work using these facilities typically develops over many subsequent years, as illustrated by specific examples given below.

<u>Impact on the development of other synchrotron facilities</u>

The success of Station 9.8 led to the design principles being used subsequently in plans for other similar facilities worldwide, particularly the beamline I19 at Diamond Light Source (DLS), effectively a direct UK replacement for Station 9.8 from 2008 [E1], and the Advanced Light Source in California, USA (ALS, conversion of beamline 11.3.1 from threatened closure in 2006 to the most productive beamline from 2009), and to the successful cases for development of these facilities as a result of its immense popularity and success. These two are the only current dedicated beamlines of their kind in the world and are unrivalled in their output by any shared-use facilities [E2, E3]; such other facilities include beamlines at APS (USA) and Soleil (France), themselves influenced indirectly by the design principles and the success of Station 9.8.

DLS is the largest UK Government-funded science project in a generation, costing around £400M in its construction to date and with an annual operating budget rising from the initial £23M in 2007–2008 as beamlines are added; it provides a high level of employment and contribution to the local economy. The I19 beamline had a construction budget of around £5M and its annual operating budget is £430K excluding support for an average of 3 PhD students per year; it has a full-time staff of 4 scientists and technical support equivalent to 1.25 FTE.

In addition to providing the model for such facilities, the original research has also produced leading scientists to manage and operate them. Of grant-funded research staff employed for the construction and commissioning stages of SRS 9.8, one is now Staff Scientist for ALS 11.3.1 (Dr Simon Teat, previously beamline scientist at SRS and Principal Beamline Scientist for DLS I19), and another is a director of the EPSRC-funded NCS (Dr Simon Coles). Major users/beneficiaries of SRS 9.8 who are now in commercial and public service employment include Dr David Allan (Principal Beamline Scientist for DLS I19), Dr Neil Feeder (Pfizer then CCDC), and Dr Elizabeth Shotton (Industrial Liaison Manager, DLS). Clegg has also helped provide training for over 150 staff and users of synchrotron facilities from many countries through Synchrotron Radiation Summer Schools, formerly at Chester/Daresbury [E4 p.69] and currently at Oxford/Diamond.

<u>Impact through commercial use of facilities</u>

Around 10 commercial companies made use of SRS Station 9.8 up to 2008, including all the major UK pharmaceutical firms; 5 companies from the pharmaceutical and chemical sectors of UK industry currently use DLS beamline I19 (one reason for the lower number is company mergers). These companies are prepared to pay full-cost-recovery commercial rates for access, since there is usually no other feasible way for them to obtain vital structural information for the development and marketing of their products when the available materials are poorly diffracting [E5]. Confidentiality agreements between the facilities and commercial customers make it impossible to provide details of such usage, but we give some examples here where results have been published or approved by company representatives, or where the work is commercially-sponsored research by academic partner teams; they are undoubtedly typical of other work. At DLS, as previously at SRS, several days of beamtime in each 6-month operating schedule are allocated to commercial work and a day of beamtime can deliver up to 10 or more data sets, as an indication of overall usage. Without the original Newcastle underpinning research, these opportunities would probably not exist and the key structures would remain unknown.

For example, Organon (now Merck) used SRS 9.8 to investigate the structure of a cyclodextrin complexed with a drug used as a neuromuscular blocker, to confirm its mode of action. Sugammadex is now marketed as Bridion; it was approved for use in the EU in 2008 and sales to date have been around £300M [E6; E4 pp. 7 & 93].

Roche Discovery Welwyn, part of Hoffman LaRoche, carried out structural studies at SRS 9.8, concentrating on active pharmaceutical ingredients, intermediates and impurities in support of anti-inflammatory and anti-viral programmes. This work contributed to the development of the influenza neuraminidase inhibitor Tamiflu (oseltamivir phosphate) and the first-generation HIV protease inhibitor Invirase (saquinavir mesylate), both originally licensed for use in the 1990s and in continued use today [E7]. Tamiflu has had particularly high public profile and impact in recent years as a major treatment during several big flu outbreaks around the world. In the UK alone the

NHS has spent an average of around £70M per year maintaining stocks of Tamiflu; annual worldwide sales peaked in 2009 and 2010 at around £550M, then reduced by over 50%.

Commercial use of the SRS facilities was taken over by DLS I19 beamline from 2009. Anhydrous sodium diclofenac was a key structure obtained by SAFC Pharmorphix (Sigma-Aldrich) using DLS I19, enabling a thorough study of relative stability of hydrates and other crystalline forms of this common painkiller, which is one of the top 100 drugs in international use, with an estimated annual value of about £820M in 2009 [E7, E8 p.5, E9]. This work is typical of polymorphism and solvate studies carried out by pharmaceutical companies, requiring synchrotron facilities for unstable and poorly crystalline forms of important drugs and drug candidates in order to secure and protect intellectual property rights attributable to particular solid forms [E7].

Other major pharmaceutical firms who have confirmed their use of these facilities in order to obtain or improve vital drug development structures and to support regulatory and patent processes are Pfizer and GlaxoSmithKlyne.

Impact through commercialisation or Government use of academic research

Zeolites and metal-organic framework materials studied by St Andrews chemists at SRS, DLS and ALS have led to Chevron Texaco patents on two materials, SSZ-23 and SSZ-51, for use in oil refineries, three patents related to storage and release of nitric oxide, and two spin-out companies, Zeomedix LLC (started in 2009 with over $1M of external investment to date) and MOFgen Ltd (started in 2013 with 14 commercial agreements with other companies) [P3, E4 p.51, E10]. Metal-organic frameworks have become popular research projects, of interest for potential in hydrogen and other gas storage and energy applications. Work is often industrially sponsored, such as that by Nottingham University supported by General Motors [E7, p.17].

ALS 11.3.1 is used in projects of the US Department of Energy, including gas separations for clean air technology, extraction of uranium from sea water, and nuclear reprocessing [E2].

5. Sources to corroborate the impact

[E1] Nowell, H., Barnett, S. A., Christensen, K. E., Teat, S. J. & Allan, D. R. (2012). I19, the small-molecule single-crystal diffraction beamline at Diamond Light Source. *J. Synchrotron Rad.* 19, 435–441

[E2] Supporting statement: Staff Scientist at Advanced Light Source (formerly Principal Beamline Scientist at SRS and at Diamond Light Source)

[E3] Supporting statement: Principal Beamline Scientist at DLS

[E4] New Light on Science: The Social & Economic Impact of the Daresbury Synchrotron Radiation Source 1981–2008. Science & Technology Facilities Council (2010). https://www.stfc.ac.uk/resources/PDF/SRSImpact.pdf

[E5] Supporting statement: Industrial Liaison Manager at DLS (and previously at SRS)

[E6] Bom, A., Bradley, M., Cameron, K., Clark, J. K., van Egmond, J., Feilden, H., MacLean, E. J., Muir, A. W., Palin, R., Rees, D. C. & Zhang, M.-Q. (2002). A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew. Chem. Int. Ed. Engl.* 41, 265–270

[E7] Supporting statement: Chief Scientific Officer at SAFC Pharmorphix Solid-State Services

[E8] Diamond Industrial Liaison Office case studies. DLS, 2013. http://www.diamond.ac.uk/Home/industry/casestudies.html

[E9] Top 200 Pharmaceutical Products by Worldwide Sales in 2009. Poster. (Diclofenac is 86th) http://cbc.arizona.edu/njardarson/group/sites/default/files/Top200PharmaceuticalProductsByWorldwideSalesin2009.pdf

[E10] Supporting statement from Professor of Chemistry, EASTCHEM, St Andrews University