Institution: University of Birmingham

Unit of Assessment: UOA 09 - Physics

Title of case study: Development of accelerator-based Boron Neutron Capture Therapy for hospital-based treatment of malignant tumours

1. Summary of the impact

Boron Neutron Capture Therapy (BNCT) is known from past clinical studies to have realistic potential to treat malignant tumours that gain only marginal benefit from other treatment approaches. In the “West”, high grade gliomas account for around 1% of cancer diagnoses, so 2000-2500 per year in the UK. The potential of this treatment will be even higher if it is extended to other tumours (e.g. in head and neck and lung). One of the factors limiting the take-up of BNCT had been a presumption that a suitable incident neutron beam could only be deployed at nuclear research reactors, which brings obvious cost and practical limitations. The work of the Birmingham group has been crucial in demonstrating that an alternative approach using an accelerator could be applied in a hospital-setting.

This approach is now being used for the first time by clinicians to implement treatment with patients. These clinical trials began in Kyoto in October 2012 and clinicians in Japan have acknowledged the research published by the Birmingham team as significant in the crucial step of designing hospital-based systems. **This allowed the development of BNCT treatment facilities which would not otherwise have been viable.** The three accelerator based facilities established in Japan are estimated to have cost £19M apiece with two more being developed, bringing additional commercial benefits to the companies that manufacture them.

2. Underpinning research

BNCT is an experimental treatment technique for cancers which are highly malignant and are infiltrating the healthy tissue around the main tumour mass. These cancers are some of the most difficult to treat and in many cases remain incurable. In particular, efforts have focussed on the infiltrating brain tumour, glioblastoma multiforme, recurrent cancers of the head and neck and metastatic cancers in liver, with pre-clinical work also looking at lung cancers. For the brain tumour patients which we have focussed upon in Birmingham, typical life expectancy after diagnosis is around 15 months, with approximately 25% of patients surviving for 2 years. Patients with these highly infiltrating tumours gain only marginal benefit from other advanced radiotherapy technologies such as Cyberknife or proton/ion beam radiotherapy.

Until the early 1990s the field of BNCT had been based exclusively around the use of nuclear research reactors to provide an incident neutron beam of the required characteristics (intensity, neutron spectrum, photon contamination etc). It was initially thought that such a neutron field could only be derived from a nuclear reactor and that this would not be possible with an accelerator driven neutron source.

The Birmingham research set-out to harness expertise gained over many years in nuclear and accelerator physics in order to find a way to use an accelerator driven source, bringing their knowledge to bear on some of the most difficult problems in cancer management.

Key outcomes of the Birmingham research effort include:

- An optimised design for an accelerator BNCT facility based on neutrons from the interaction of 2.8 MeV protons with a lithium metal target.
- A design and proof of successful operation of a high power lithium metal target where the lithium remains solid for beam-powers of the order of 4.5kW.
- Experimental data to confirm simulations at low and high beam powers, and a demonstrated capability to deliver clinical treatments in a possible treatment time.

Overall the Birmingham effort delivered 10 journal papers between 1995 and 2004, numerous conference papers and presentations and the completion of 8 PhD projects. The work in Birmingham still continues with more recent conference and journal papers, and 2 PhD students completed their projects during 2012. All of these provide mechanisms by which the impact of the work in Birmingham was generated.

The key researchers over this period in Birmingham were Prof T Derek Beynon (Head of Group, retired in 2002), Dr Dennis Allen (Research Fellow, School of Astronomy and Physics, Feb 1992 to June 2000) and Stuart Green (Honorary Research Fellow, School of Physics and Astronomy from Feb 1993, now Hon Professor from Feb 2011; also Clinical Scientist at University Hospital Birmingham). There was also strong support and clinical leadership from Professors Nicholas James (School of Cancer Studies) and Garth Cruickshank (Department of Neurosurgery Queen Elizabeth Hospital).

3. References to the research

Publications from the physics component of the Birmingham team have been mainly in the two Internationally leading journals of this field; these are the UK journal, *Physics in Medicine and Biology*, and the US journal, *Medical Physics.* Those listed here best exemplify the quality of this research. The Culbertson paper demonstrated the viability of an accelerator-based approach. The main journal paper from Birmingham which has been highly cited is

1. D A Allen and T D Beynon 1995 *A design study for an accelerator-based epithermal neutron beam for BNCT*, *Phys. Med. Biol.* **40** 807: doi:10.1088/0031-9155/40/5/007

Papers published over the next few years showed experimental validation of the design calculations, and some evolutions and improvements in the design of a beam facility:

2. D. A. Tattam, D. A. Allen, T. D. Beynon, G. Constantine, M. C. Scott, and D. R. Weaver, S. Green 1998*. In-phantom neutron fluence measurements in the orthogonal Birmingham boron neutron capture therapy beam*, Med. Phys. **25**, 1964 (1998): http://dx.doi.org/10.1118/1.598386

3. D. A. Allen and T. D. Beynon, S. Green, N. D. James (1999). *Toward a final design for the Birmingham boron neutron capture therapy neutron beam*. Med. Phys. **26**, 77: http://dx.doi.org/10.1118/1.598480

4. D. A. Allen and T. D. Beynon (2000). *What is the best proton energy for accelerator-based BNCT using the $^{7}Li(p,n)^{7}Be$ reaction?* Med. Phys. **27**, 1113: http://dx.doi.org/10.1118/1.598976

The paper which demonstrated that the Birmingham accelerator could indeed produce clinically useable beam intensity is:

5. C N Culbertson, S Green, A J Mason, D Picton, G Baugh, R P Hugtenburg, Z Yin, M C Scott, J M Nelson (2004). *In-phantom characterisation studies at the Birmingham Accelerator-Generated epithermal Neutron Source (BAGINS) BNCT facility*. Applied Radiation and Isotopes, Volume 61, Issue 5, 733–738: http://dx.doi.org/10.1016/j.apradiso.2004.05.057

The quality of the underpinning research is best illustrated by publications 1, 2 and 3.

4. Details of the impact

BNCT is a non-invasive treatment of locally invasive malignant tumours such as primary brain tumours. It involves the injection with a tumour localising drug containing boron (boron-10) and subsequently the patient is exposed to a flux of epithermal neutrons which are scattered (reduced in energy) and then preferentially captured by the boron. The boron-11 produced then undergoes fission efficiently, depositing a large amount of energy within the tumour cells, destroying them.

The impact of the research undertaken by the Birmingham group has been through identifying an effective accelerator-based neutron source (ABNS). Without such a source, the use of the therapy would continue to be limited to the small number of suitable nuclear research reactors. The Birmingham Group's pioneering research has enabled and encouraged clinicians at University Hospital Birmingham and in other countries, such as Japan, Argentina and Israel, to progress towards the introduction of hospital-sited BNCT treatments, developments that have extended over the period 2008 to 2013. There is strong evidence to indicate that this advance would not have taken place without the Birmingham Group's research findings.

The most advanced stage of hospital-based application of BNCT has been achieved in Japan and it has been confirmed that the first clinical trial of the therapy using an accelerator-based neutron source began in Kyoto in October 2012.

Contribution of Birmingham's research to the development of accelerator-based sources: The key contribution made by researchers at Birmingham was to demonstrate the possibility for real clinical treatments using an accelerator-based source. This was crucial in encouraging developments from other research groups and manufacturers alike in different parts of the world. The initial idea of accelerator BNCT came from Prof Jacqueline Yanch at MIT and by Prof Thomas Blue at Ohio State University in the 1990s. However, the key to its application was to demonstrate that these ideas were practical and this work was performed by Prof Derek Beynon's group in Birmingham. The paper by Allen and Beynon published in 1995 in Physics in Medicine has been cited over 50 times in the subsequent scientific literature. It was this practical demonstration that was necessary to engage a wider clinical interest. The paper by Culbertson et al from the Birmingham group in 2004 showed experimental data at realistic (although still lower than desirable) clinical beam powers. The treatment times shown in the Culbertson paper are similar to those experienced by approximately 30 patients treated with the reactor beam at MIT. This was a crucial step in opening up the option of hospital-based treatment using BNCT, thereby encouraging further clinical interest.

Importance of accelerator-based neutron sources (ABNS) in adoption of BNCT: Assessments of the application of BNCT now acknowledge that availability of accelerator-based sources are essential if the treatment is to be widely applied; for instance, a recent review of 20 years' experience of BNCT in Finland published in *Physica Medica* concluded: "... *we recognise that there is no doubt that realizing ABNS is one of the determining factors in how fast BNCT will be established as routine clinical treatment*." [1] A review undertaken in 2007 for the Australian government had noted the extremely prohibitive costs of providing the treatment if this was reliant on access to a reactor-source. [2]

International take-up of the Birmingham findings: Currently (2013), the most advanced stage in the hospital-based application of BNCT is being achieved in **Japan**, and this progress has been explicitly linked by the development team there to the Birmingham findings. **The first patients have now been treated (since October 2012) on the Sumiton cyclotron system in Kyoto** [3].

[redacted], President of the International Society for Neutron Capture Therapy and Chairman, Department of Neurosurgery, University of Tsukuba, has said: "*Owing to the Birmingham research activity, several new projects on accelerator based BNCT has been recently started. There are now three accelerator projects in Japan, namely, KURRI with Sumitomo Heavy Industrial Co Ltd, University of Tsukuba+KEK+JAEA with Mitsubishi Heavy Industrial Co Ltd and National Cancer Research Center with a venture company*". [4] The construction of these facilities was completed in 2013.

The Japanese government is investing heavily in BNCT, with a vision to treat the most difficult cancers in a single treatment session. Gaining high level support for such a vision requires strong clinical leadership, which comes from some excellent clinicians in Japan, and an understanding that what is required is actually deliverable, which comes from the pioneering work in Birmingham. Investment is made to construct BNCT treatment facilities in Universities, research laboratories and hospitals across Japan. For example, in March 2013 an accelerator has been ordered from Sumitomo Heavy Industries, Ltd for installation in Fukushima for BNCT treatment. The cost of construction of the BNCT facility is estimated to be at least £19M [5].

An **Israeli** team at the **Soreq Applied Research Accelerator Facility** has reached the stage of a viable liquid lithium accelerator target and are now constructing the accelerator facility that will exploit this.

In **Argentina** efforts continue to develop a new accelerator device to deliver BNCT which has been supported by Birmingham's work[redacted] Professor of Physics and Head Accelerator Technology and Applications Department, Comision Nacional de Energia Atomica has confirmed that "*the Birmingham machine has been for many years the only one delivering an intense proton beam and hence a sufficiently strong neutron beam to make realistic work in AB-BNCT. This attracted our attention and finally led to a fruitful collaboration between Birmingham and Buenos Aires around the possibility of developing a SPECT system specifically designed for BNCT*". The results of this work have been published by the Argentine team [6].

Clinical Work in the UK: Clinical research has focussed on the optimisation of boron uptake in tumours. This has included clinical research studies involving patients already undergoing treatment at the University Hospital Birmingham. Currently, clinical studies are on-going at the hospital into a new form of the boron carrier compound boron phenylalanine which has been specially re-formulated for studies in Birmingham by Cancer Research UK. While this is still a research study with important outputs in the scientific literature (see for example Detta and Cruickshank, Cancer Res 2009), the studies take place in the neurosurgery theatres of University Hospital Birmingham and involve patient volunteers. The existence of these studies show the on-going impact of the Birmingham research through continued interest in the various aspects necessary to eventually introduce the treatment. Without the relationship between the Birmingham Physics Group and the University Hospital it is doubtful that there would be active BNCT programme in the UK.

There is a close relationship between the Birmingham Group and University Hospital Birmingham. As a result of this collaboration, the University is using its Dynamitron accelerator, manufactured by IBA (a Belgian company), adapted for BNCT by the Birmingham team. This has enabled the University to attract external support from Cancer-Research UK for the only on-going research in Britain on the hospital-based application of BNCT. The accelerator is currently being adapted for clinical trials.

Overall impact: The Birmingham group was the first to show practically that it was possible to use an accelerator to produce a beam with the necessary characteristics for these purposes. The impact has been felt across the development community where there is now documented acknowledgement that accelerator-based sources are part of the primary development route for this therapy. The Birmingham research has made the treatment economically viable and equivalent to existing radiotherapy facilities – which would not have been the case with a reactor based facility. The significance of the Birmingham group's work has been in demonstrating a practical method of using BNCT in clinical settings with evidence set out here that this approach is now being actively applied in a number of countries. The key beneficiaries of this research will be patients treated with BNCT from an accelerator neutron source**. Patients have now been treated on the Sumiton cyclotron system in Kyoto.** This should also happen soon in both Tokyo and Fukushima. In the "West", high grade gliomas account for around 1% of cancer diagnoses, so 2000-2500 per year in the UK. The potential of this treatment will be even higher if it is extended to other tumours (e.g. in head and neck and lung). There is thus significant societal benefit from the developments described here. There is also demonstrable commercial impact within the REF period is to companies such as Sumitomo Heavy Industrial Co Ltd and Mitsubishi Heavy Industrial Co Ltd who constructed the facilities which will perform the treatment, with each facility estimated to cost at least £19M [5].

5. Sources to corroborate the impact

[1] Savolainen S, et al., Boron neutron capture therapy (BNCT) in Finland: Technological and physical prospects after 20 years of experiences, Physica Medica (2012), doi:10.1016/j.ejmp.2012.04.008

[2] Australian and New Zealand Horizon Scanning Network, *Boron Neutron Capture Therapy for Cancer Treatment,* Australian Govt Department of Health and Ageing, October 2007, p.7

[3] Communication from [redacted] Kyoto University Research Reactor Institute

[4] Communication from [redacted], President of International Society for Neutron Capture Therapy, Chairman, Dept of Neurosurgery, University of Tsukuba, Japan

[5] Nakagawa et al., Applied Radiation and Isotopes 67(2009)S80–S83

[6] letter from [redacted] dated 11/7/2012

Evidence of ongoing projects around the World developing BNCT as a clinical modality based on accelerators: : Argentina : http://escholarship.org/uc/item/4w92t24t ; Japanese Accelerator projects: http://kokusai.kek.jp/istc/p/Mori.pdf; Israel: http://www.linac12.org.il//Research.ehtml, http://www.shi.co.jp/english/info/2012/6kgpsq0000001jc0.html