Institution: University of Birmingham

Unit of Assessment: UoA 9, Physics

Title of case study: Transforming Treatment of Otherwise Incurable Cancers Through Accelerator-based Boron Neutron Capture Therapy

Period when the underpinning research was undertaken: 2000–2012

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof. Stuart Green	Honorary Senior Research Fellow/Honorary Professor	1992–present
Dr Malcolm Scott	Senior Lecturer	Honorary from 1991–present
Prof. John Hopewell	Honorary Professor	1996–2009

Period when the claimed impact occurred: 2014–2020

Is this case study continued from a case study submitted in 2014? Yes

1. Summary of the impact

Boron Neutron Capture Therapy (BNCT) has become a viable treatment option for the most aggressive cancers, with impact on **global commerce and the economy**, and on **patient outcomes**, because of our research. We directly contributed to **innovation and commercial activity** at the international medical equipment company, Neutron Therapeutics, which **developed a major new product** (a clinical BNCT facility). We provided companies with the confidence to **invest in and adopt new clinical BNCT technology**, indirectly **reducing risk** for the Japanese company, Cancer Intelligence Care Systems (¥5 billion investment) and influencing the **strategic investment** ($70 million) of the multi-national company, TAE Life Sciences, to expand its business into BNCT therapeutics. **BNCT has been approved as a treatment option** for recurrent head and neck cancers in Japan. It not only **improves patient survival** but also requires **less treatment time at lower cost** than other advanced forms of radiotherapy.

2. Underpinning research

Our research was the first to produce a clinically suitable treatment beam using an accelerator for Boron Neutron Capture Therapy (BNCT), a step-change in the field.

Developing BNCT to safely treat glioblastoma multiforme, and head and neck cancers

The potential of BNCT to treat otherwise incurable cancers has been understood for decades, but was never practical until our breakthroughs. Effective treatment depends on the interaction of a non-toxic boron-containing drug, which is selectively absorbed by cancerous cells, and a neutron beam. The challenge we faced was that only a nuclear reactor could produce the neutron beam. This was too expensive and hazardous to install in a hospital. Moreover, the beam it produced could contain high-energy neutrons that might have damaging side effects. To make BNCT practical, the beam would need to be instead produced by a particle accelerator.

This presented **2 significant challenges, both of which we overcame**.

Key finding 1 [KF1]: Producing a safe and practical lithium target
First, to produce a neutron field, we must fire protons at a lithium 'target'. However, this produces heat that would melt the lithium if not controlled. Bonding the lithium with copper allows

heat to conduct through the copper to water. This requires the lithium and copper to stay bonded under the powerful heating caused by proton bombardment.

We developed a new and powerful technique to achieve effective bonding of the lithium and copper and in 2004 demonstrated its effectiveness [S1]. The image below shows sections through an un-treated Li-Cu junction on the left and on the right a typical bond that our process achieves. Here lithium (on the right half of the right image) has partially diffused into the copper (on the left). This forms a strong bond which allows heat to be removed from the lithium while it remains solid under proton beam powers of approximately 3–4kW. **Before our work, this was widely viewed as an extraordinarily challenging problem that might never be solved.**

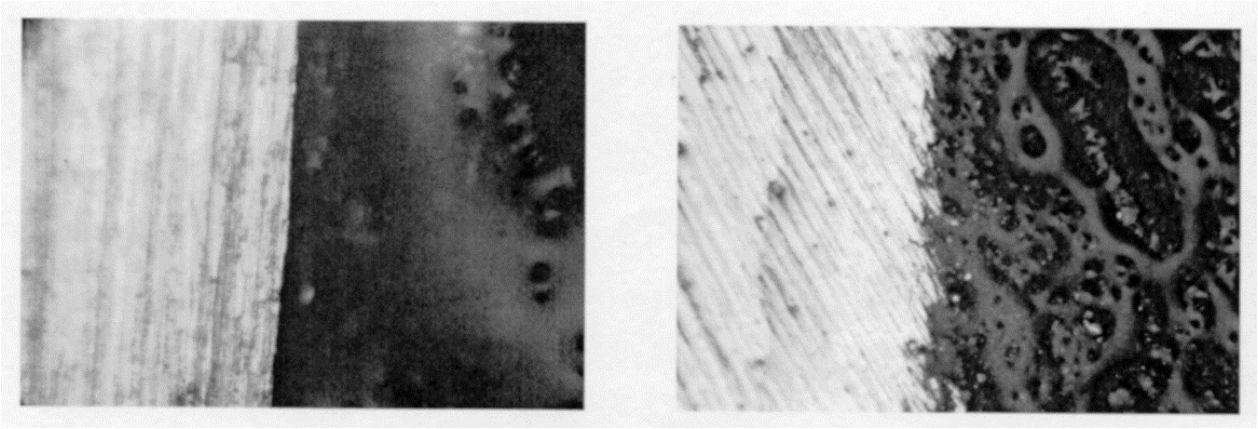

Image 1: L showing the untreated Li-Cu junction; R showing Li-Cu diffusion after treatment.

Key finding 2 [KF2]: Developing a sufficiently intense and less contaminated narrow spectrum neutron beam for clinical application
Secondly, having produced a neutron field, we converted it into a beam suitable for treating patients, using what is termed a Beam Shaping Assembly (BSA). The combination of accelerator and BSA can be used to produce a narrower spectrum neutron beam, reducing unwanted high-energy neutrons that would otherwise damage the patient.

In 2003/4, **we demonstrated for the first time that this combination of equipment would produce clinically usable dose-rates** [S1]. We showed how the target and BSA had worked reliably over a period of months to allow characterisation of the beam by both physical dosimetry and a limited programme of cell radiobiology. This paper [S1] brings together our work to demonstrate performance of the lithium target and of the characteristics of the radiation field for patient treatment.

Key finding 3 [KF3]: Demonstrating greater protection for healthy tissues using the accelerator beam
Finally, we developed an improved understanding of the biological consequences of the mixed radiation field delivered during BNCT treatment. This work demonstrated that the components of a mixed radiation field undergo a synergistic interaction that produces a greater cell kill effect than would be anticipated from the independent action of the different radiation types [S2]. We also demonstrated the **reduced biological effects of our accelerator beam** compared with the established Studsvik reactor beam for BNCT which had previously been used for patient trials [S3].

3. References to the research

[S1] Culbertson, C.N., Green, S., Mason, A.J., Picton, D., Baugh, G., Hugtenburg, R.P., Yin, Z., Scott, M.C., Nelson, J.M. 2004. In-phantom characterisation studies at the Birmingham Accelerator-Generated epithermal Neutron Source (BAGINS) BNCT facility. *Applied Radiation and Isotopes*, 61(5), 733–738. DOI: 10.1016/j.apradiso.2004.05.057.
[S2] Phoenix, B., Green, S., Hill, M.A., Jones, B., Mill, A., and Stevens, D.L. 2009. Do the various radiations present in BNCT act synergistically? Cell survival experiments in mixed alpha-particle and gamma-ray fields. *Applied Radiation and Isotopes*, 67(7–8), S318–S320. DOI: 10.1016/j.apradiso.2009.03.097.

[S3] Mason, A.J., Giusti, V., Green, S., af Rosenschöld, P.M., Beynon, T.D., and Hopewell, J.W. 2011. Interaction between the biological effects of high- and low-LET radiation dose components in a mixed field exposure. *International Journal of Radiation Biology*, 87(12), 1162–1172. DOI: 10.3109/09553002.2011.624154.

4. Details of the impact

Four international companies are now **producing accelerator-based BNCT equipment** as a direct consequence of our key findings (Neutron Therapeutics, Cancer Intelligence Care Systems (CICS), TAE Life Sciences and Sumitomo Heavy Engineering). This has led to **economic and commercial impact** of 2 distinct types: (1) **innovation and new product development** at international medical equipment companies (clinical BNCT facilities); and (2) the **adoption of** and investment in **new BNCT technologies** at facilities around the world. The significance of these developments is further attested by the demonstrable **improvement in patient outcomes** shown in multiple clinical trials internationally.

1) Enabling the development of a new product, a fully formed and bespoke clinical BNCT facility, by international medical equipment companies

The medical equipment company, Neutron Therapeutics, **developed a clinical BNCT facility as its main commercial product** using the specific lithium-copper bonding approach that we developed [KF1] in its manufacturing process. Its prototype has been demonstrated at 10s of kW of proton beam power for hundreds of hours run time with no degradation. Neutron Therapeutics' Chief Operating Officer asserted that "The Birmingham team solved th[e] problem [of physical and thermal bonding of the lithium layer to a suitable substrate] for a copper target backing material and **we have followed this approach for our commercial product**. It is a critical aspect of our system and under-pins the success of our product" [E1].

The Tokyo-based company CICS is a major partner in the **creation of a new BNCT facility**, using a safe lithium target design, at the National Cancer Centre (NCC) in Tokyo, Japan. The NCC is the largest specialist cancer treatment hospital in Japan and spearheads standardising cancer treatment in the country. Our demonstration that the neutron beam produced by a proton beam hitting a lithium target reduced damaging side effects [KF3] materially contributed to CICS's adoption of the lithium target technology to create the facility. Its President and CMO commented that these benefits "convinced us that the choice of a lithium target was the right one for our project" [E2], significantly **influencing the commercial activity** and **strategic direction** of the company.

The development of these BNCT facilities are materially dependant on the work of the University of Birmingham team, whose research [KF1, KF2] gave the funders confidence such that, since 2012, the NCC BNCT project has received extensive and sustained investment. It took CICS 8 years to build the equipment prototype CICS-1, at a cost of ¥2 billion, and our research [KF1 and KF2] served specifically to **ensure stakeholder confidence** and reassure investors that the final goal was achievable. CICS confirmed that our research **reduced its financial risks**: "The achievements of the team in Birmingham to produce a functioning BNCT system with a lithium target were critical for our project. They enabled us to provide the reassurance that our stakeholders required" [E2]. To date the **NCC has spent ¥5 billion** on the building construction and **BNCT equipment**. Following the success of the NCC BNCT project, CICS will deliver a second BNCT facility for Edogawa Hospital, Tokyo in March 2021.

2) Through the use of BNCT, new clinical technologies, in the form of new therapies, were developed

We have contributed to **innovation within the international BNCT community**, which has used our pioneering research findings [KF1–KF3] to **develop BNCT therapies**, with excellent efficacy. In addition to Neutron Therapeutics, which uses our specific lithium-copper bonding approach [KF1], three companies, TAE Life Sciences, Cancer Intelligence Care Systems (CICS) and Sumitomo Heavy Engineering, **developed BNCT technology only after we had demonstrated that accelerator-BNCT was possible**. Indeed, our research was described by the President of the International Society for Neutron Capture Therapy as "crucial in enabling

BNCT as a medical therapy for incurable cancers. Motivated and inspired by (our) research, new accelerator projects have been initiated in Japan, Europe and around the World" [E3].

The Boston-based company Neutron Therapeutics, established in 2014, uses our lithium-copper bonding technique [KF1]. The company employs 25 people. In 2019, their **first full clinical system was commissioned** by the Helsinki University Hospital team to initially treat patients with recurrent head and neck cancers. The facility has the capacity to treat up to 2,000 patients per year. A second system will be deployed at Shonan Kamakura General Hospital in Kanagawa, Japan, in 2021. The approximate value of each clinical facility is $25 million. In 2020, Neutron Therapeutics received an additional order for an accelerator neutron source for research in the UK [E1].

Our ability to demonstrate the feasibility of BNCT as a viable clinical treatment [KF1 and KF2] impacted the **commercial opportunities and investment strategy** of the multi-national company, TAE Life Sciences. TAE Life Sciences **raised $70 million** in funding to launch a subsidiary of the nuclear fusion energy company TAE Technologies in 2018 [E4, E5]. This significant strategic investment aims to commercialise BNCT with its accelerator-based technology, making neutrons for BNCT more accessible in hospitals and hence indirectly providing better treatment for patients with incurable cancers [E4]. The company is supplying equipment to the NeuBoron facility at Xiamen Humanity Hospital in China. Construction of this facility is nearing completion and accelerator equipment is currently being installed. It will treat the first patients in 2021. In total, 14 facilities are in development or at clinical trial stage, in 8 counties around the world [E6].

New therapies are being developed using the new BNCT clinical facilities, in which CICS has invested, exploring new indications for BNCT [KF1–KF3]. These include sarcoma, malignant melanoma and pleural mesothelioma [E2]. Because of the low toxicity of the lithium target neutron beam, the CICS team are actively exploring the use of BNCT in the treatment of Alzheimer's disease. The President and CMO commented that "I am deeply grateful to Professor Green's prototype for guiding our developments" [E2].

The Japanese company Sumitomo Heavy Industries has also invested in BNCT facilities for therapeutic purposes, at Kyoto University Research Reactor Institute and 2 treatment rooms each at the Southern Tohoku General Hospital (Koriyama) and Osaka Medical College. In March 2020, the Japanese Ministry of Health, Labor and Welfare **approved the Sumitomo accelerator system of BNCT** as a treatment for patients with recurrent head and neck cancers [E7].

3) Demonstrable improvements in patient outcomes, treatment time and costs

The **efficacy of BNCT has been demonstrated** by multiple clinical studies by research teams internationally. The benefits of BNCT take 3 forms: the first is **improved patient survival** (points i–iii, below), the second is **reduced toxicity** (point iv) and the third is reduced treatment time and consequently costs (point v).

i) Patients with newly diagnosed glioblastoma multiforme: These brain tumours are both radio-resistant and highly infiltrating, and while the incidence is relatively low (around 4,500 cases per year in the UK), poor outcomes mean that it results in the most years of life lost of any single tumour type. Clinical results from Japan show that patients with newly diagnosed glioblastoma multiforme treated with **BNCT could achieve a 2-year survival rate of 50% compared to ~30% for the best available conventional treatments** [E8]. By extension, if all the ~4,500 cases per year in Britain were treated with BNCT, it would raise the number of patients alive at 2 years from ~1,350 (with conventional treatments) to 2,250. This can be extrapolated to the annual global incidence of ~200,000.

ii) Patients with glioblastoma multiforme that has recurred after first-line treatment has failed: For patients where the disease recurs and where patients are fit enough for a second-line treatment, recent data presented by a team in Japan suggests that survival at 1 year following **BNCT treatment with an accelerator neutron source could approach 80% (compared with an expectation of ~35% with standard approaches)** [E9]. This is a huge difference.

iii) Patients with head and neck cancers that have recurred after first-line treatment has failed: In the UK, around 12,000 patients are diagnosed with head and neck cancers each year and ~45% of these will suffer a relapse within 5 years of treatment. Conventional treatments are often so toxic that clinicians are reluctant to repeat them and so offer patients only palliative treatment and pain relief. In some regions of China, the incidence of these cancers is dramatically higher than in the UK. Trial data from Helsinki [E10] has inspired many centres, including a number of those above, to pursue BNCT. Further analysis from the Helsinki team, published in 2019 showed **~46% of patients with recurrent cancers in the head and neck to have survived 2 years following BNCT treatment and over 20% surviving 5 years** [E11].

iv) Reduced toxicity: Unlike many existing treatments, BNCT shows both good disease control and low toxicity for patients with head and neck cancers. That means that BNCT can be used safely following intensive first-line treatment and can even be repeated multiple times should the disease recur (Kato *et al*. where BNCT treatment was repeated 3 times for 1 patient [E12]). Accelerator BNCT is even less damaging to healthy tissues [KF3] than is demonstrated in these studies which are based on neutron beams from nuclear reactors.

v) Reducing treatment time and costs: The overall **benefits of using BNCT over conventional proton radiotherapy treatments** are considerable. A single BNCT treatment room costs the same as a single-room proton radiotherapy facility (approximately $25 million), but can treat substantially more patients. Patients undergoing BNCT only require 1 or 2 or treatment sessions (as opposed to between 5 and 30 for proton radiotherapy) and each session only takes between 20 and 30 minutes. This means that each facility has the **capacity to treat at least ~6 times more patients per year**, ~2,000 in total [E1]. **This simultaneously cuts capital-cost-per-patient significantly and provides better clinical outcomes** than are possible with protons. Neutron Therapeutics confirmed that "[i]t is our view that this cost-effectiveness, combined with the potential to improve outcomes for patients, will lead to a significant expansion in BNCT treatment capacity in the coming years" [E1].

5. Sources to corroborate the impact

[E1] Testimony from the Chief Operating Officer of Neutron Therapeutics (dated 14/12/2020).
[E2] Testimony from the President and CMO of Cancer Intelligence Care Systems (dated 23/12/2020).
[E3] Testimony from the President of the International Society for Neutron Capture Therapy (dated 19/10/2019).
[E4] '$40 million for boron neutron capture therapy', *Chemical and Engineering News*, 96(12), 19 March 2018 [accessed 26/11/2020].
[E5] 'TAE Life Sciences secures $30M in initial B round to accelerate development of unique boron delivery drugs for novel cancer treatment, boron neutron capture therapy (BNCT)', June 2020 [accessed 11/12/2020].
[E6] Kiyanagi, Y. *et al*. 2019. "Status of accelerator-based BNCT projects worldwide", *AIP Conference Proceedings* 2160, 050012. DOI: org/10.1063/1.5127704.
[E7] 'Sumitomo Heavy Industries, Ltd. obtains medical device approval for manufacturing and sales of accelerator based BNCT system and the dose calculation program in Japan' [accessed 26/11/2020].
[E8] Yamamoto, T. *et al*. 2009. Boron neutron capture therapy for newly diagnosed glioblastoma. *Radiotherapy and Oncology*, 91, 80–84. DOI: 10.1016/j.radonc.2009.02.009.
[E9] Miyatake, S-I. *et al*. 2020. Accelerator-based BNCT in rescue treatment of patients with recurrent GBM: A multicenter phase II study. *Journal of Clinical Oncology*, 38(15), 2536. DOI: 10.1200/JCO.2020.38.15_suppl.2536 [accessed 8/1/2021].
[E10] Kankaanranta, L. *et al*. 2007. Boron Neutron Capture Therapy in the Treatment of Locally Recurred Head and Neck Cancer. *International Journal of Radiation Oncology*Biology*Physics*, 69(2), 475–482. DOI: 0.1016/j.ijrobp.2007.03.039.
[E11] Koivunoro, H. *et al*. 2019. Boron neutron capture therapy for locally recurrent head and neck squamous cell carcinoma: An analysis of dose response and survival, *Radiotherapy and Oncology*, 137, 153–158. DOI: doi.org/10.1016/j.radonc.2019.04.033.
[E12] Kato, I. *et al*. 2004. Effectiveness of BNCT for recurrent head and neck malignancies, *Applied Radiation and Isotopes*, 61(5), 1069–73. DOI: 10.1016/j.apradiso.2004.05.059.