

Institution: University of Huddersfield		
Unit of Assessment: UoA5		
Title of case study: Prevention of Chemotherapy-Induced Hair Loss Through Scalp Cooling: Transforming Patient Wellbeing by Providing the Evidence Base for Worldwide Roll-Out		
Period when the underpinning research was undertaken: 2011 onwards		
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:
Dr Nik Georgopoulos Dr Andrew Collett	Reader Senior Lecturer	2008 onwards 2008 onwards
Period when the claimed impact occurred: 2014 onwards		
Is this case study continued from a case study submitted in 2014? No		
<p>1. Summary of the impact</p> <p>For many cancer patients, chemotherapy-induced hair loss (alopecia) represents the most feared and traumatic aspect of their treatment. The only available method to combat alopecia is scalp cooling. Researchers at the University of Huddersfield have provided the evidence base for this technology and were instrumental in Paxman, a Yorkshire-based small British SME specializing in scalp cooling, becoming the world's leading provider in this field and obtaining clearance for a medical device from the US Food and Drug Administration (FDA). As a result, by 2020 Paxman had 70% of the global scalp cooling device market and supplied 98% of NHS Trusts and private providers in the UK, along with a further 53 countries. This meant that the technology became available to around 80,000 patients per year globally, proving "psychologically monumental" for many in improving their quality of life during treatment.</p>		
<p>2. Underpinning research</p> <p>In 2018, ~18.1 million people were diagnosed with cancer worldwide; this is set to increase to 29.4 million by 2040. Approximately 20% (3.6 million in 2018) of patients were eligible for a chemotherapy regime that can cause alopecia; to ~70% of patients, such hair loss represents the most feared and traumatic side-effect, with some even refusing life-saving treatment for this reason. The only known way of preventing chemotherapy-induced hair loss is scalp cooling. In the 1990s, Paxman – a company based in Huddersfield that originally made cooling systems for breweries, but began to take an interest in scalp cooling when the CEO's mother contracted cancer – started to design the first scalp cooling systems. However, it was only known empirically that scalp cooling can reduce alopecia in cancer patients undergoing chemotherapy; there was no scientific underpinning. This complete lack of biological evidence caused resistance to its use by clinicians, as well as regulatory barriers, notably lack of clearance by the US Food and Drug Administration (FDA), meaning that the Paxman device was unable to enter the lucrative American market. These factors were major obstacles to increasing the availability of scalp cooling.</p> <p>In 2011, Paxman approached Dr Nik Georgopoulos (Reader) and Dr Andrew Collett (Senior Lecturer, both at Huddersfield since 2008), who have research expertise in epithelial physiology (cell proliferation/apoptosis), cancer biology, and cellular drug delivery and uptake, and led the research described below. Their ground-breaking research was the first to provide direct biological evidence that cooling "rescues" cells of the hair follicles from chemotherapy drug-mediated toxicity, and allowed the researchers to elucidate the mechanisms by which cooling protects.</p> <p>Using in-vitro cell models, the researchers examined the effect of chemotherapy drugs on cells from human hair follicles and tested the ability of cooling to protect from cytotoxicity. This work highlighted the importance of temperature for adequate protection: a difference of just 3–4°C was shown to be critical. It had previously been hypothesized that the target temperature of 22°C could maximally protect from toxicity; yet the research demonstrated that lowering the temperature to 18°C dramatically reduced the cytotoxicity of chemotherapy drugs [2011–2013; Section 3 Output 1].</p>		

Georgopoulos and Collett expanded upon these findings by carrying out extensive in vitro testing (2014–2015) to ascertain the ability of cooling to protect against a large number of the most common chemotherapy regimens. Their research team, therefore, continued to provide drug-specific data used by the company to help inform clinical recommendations about the efficacy of cooling for different drugs, whilst also significantly enhancing the accessibility of biology-based (in vitro) evidence supporting the efficacy of scalp cooling to relevant clinical professionals [2017–2018; Output 2].

Following that, the researchers elucidated which intracellular signalling events that trigger toxicity in response to chemotherapy drugs are specifically attenuated by cooling, as well as showing that cooling protects, at least in part, due to its ability to directly suppress cellular uptake of chemotherapy drugs [2017–2019; Output 3].

Georgopoulos and Collett also discovered that for some individuals, the scalp does not cool adequately to reach the “optimal” temperature for protection, which may explain why for some patients scalp cooling is less effective. This observation, together with the deeper understanding of the precise cellular mechanisms by which optimal cooling rescues cells resulting from the research, prompted them to carry out experiments to understand how the inefficacy of “sub-optimal” cooling can be overcome. They then developed a novel (patented) methodology to reduce cytotoxicity at “sub-optimal” temperatures [2018–2020; Output 4]. Developing this intervention (combination of cooling with a topical agent) and the route to its clinical testing is a central research theme of the Paxman Scalp Cooling Research Centre (PSCRC) at Huddersfield University, which was established in February 2019 with Dr Georgopoulos as PI.

Part of the research described was funded by a two-year KTP grant (2013–15, £115,000), which was awarded the highest rating of “**Outstanding**” by the Technology Strategy Board (TSB, now Innovate UK).

3. References to the research

Research outputs below include peer-reviewed articles (min. 2* quality) in journals that are well-recognised platforms for wide accessibility by open access (PLOS One article) and /or highly prominent in their fields (The Oncologist), and an international patent submission.

[Output 1] Al-Tameemi W, Dunnill C, Hussain O, Komen MM, van den Hurk CJ, Collett A, Georgopoulos NT. (2014). Use of in vitro human keratinocyte models to study the effect of cooling on chemotherapy drug-induced cytotoxicity. *Toxicol In Vitro*. 28: 1366-76. (<https://doi.org/10.1016/j.tiv.2014.07.011>) – *this 2* research article is the first biological evidence supporting the ability of cooling to protect hair follicle cells from chemotherapy drug-induced cytotoxicity and demonstrates how only a few (3–4) degrees in temperature has a marked impact in achieving protection from toxicity.* [output relates to TSB award – Section 2].

[Output 2] Dunnill CJ, Al-Tameemi W, Collett A, Haslam IS, Georgopoulos NT. (2018). A Clinical and Biological Guide for Understanding Chemotherapy-Induced Alopecia and its Prevention. *The Oncologist*. 23:84-96. <https://doi.org/10.1634/theoncologist.2017-0263> – *albeit a review article, this represents the first complete guide of the clinical and biology-based (in vitro) evidence supporting the efficacy of scalp cooling, and for the first time makes the science supporting scalp cooling accessible and understandable to oncologists and nurses.*

[Output 3] Dunnill C, Ibraheem K, Peake M, Ioannou M, Palmer M, Smith A, Collett A, Georgopoulos NT. (2020). Cooling-mediated protection from chemotherapy drug-induced cytotoxicity in human keratinocytes by inhibition of cellular drug uptake. *PLOS One*. 15(10): e0240454 (<https://doi.org/10.1371/journal.pone.0240454>) – *this 2* research article represents the first biological demonstration that cooling inhibits the uptake of chemotherapy drugs by hair follicular keratinocytes.*

[Output 4] International Patent Application No. [PCT/GB2017/051804](https://patents.google.com/patent/PCT/GB2017/051804) -- Composition and Apparatus for Treatment of Chemotherapy Induced Alopecia – *this patent submission relates to the principle of combination of scalp cooling and topical treatment (Georgopoulos and Collett are named investigators on the patent).*

4. Details of the impact

Summary: The research has led to very significant steps towards making scalp cooling available to cancer patients globally, notably licensing by the FDA, opening up the lucrative US and other international markets. For Paxman, the commercial impact has almost quadrupled both its turnover and staffing. Nearly 80,000 patients per year have been given access to a system which – as many testify – has had a huge impact on their emotional well-being and quality of life.

International recognition, licensing and marketing of scalp cooling:

Central to Paxman obtaining international licensing was the FDA requirement to demonstrate how scalp cooling works before they would approve the necessary clinical trial. The experimental data supplied by the Huddersfield research was central in facilitating this and was cited in the FDA application [Section 5, source #3]. As a result, in 2017, Paxman became one of the few British SMEs to obtain FDA clearance for a medical device, opening up the lucrative US and other markets (e.g. South America and Japan). By the end of 2020, the scalp cooling machines were being exported to over 50 countries, greatly increasing the potential market and patient numbers with access to scalp cooling: at this point, Paxman had ~500 systems in 259 locations across 37 US States and 50 new systems in Japan [#7], figures which were continually expanding. CEO Richard Paxman emphasized the high significance of FDA approval in an interview with US online publication Cure Today in April 2017: “The clearance of our Paxman scalp cooling system has a huge impact. We are excited now to be in a position to roll out equipment throughout the US” [#10d].

Commercial impact on Paxman business growth, innovation and strategy:

The biological discoveries supplied by the Huddersfield researchers were pivotal in stimulating Paxman to make the strategic decision to not only move towards personalized cap design for more effective scalp cooling, but also to improve the device (with a re-designed refrigeration unit) so that it was better at heat-extraction.

As a result of the research and the subsequent FDA approval, between 2013 and 2019 Paxman increased its annual turnover from ~£2million to >£9million, the proportion of exports increased from 40% to ~85% and its employees from 12 to 45 (2019), which more recently increased to 48 [#7]. Paxman exported its scalp cooling systems to 53 countries, giving it 70% of the global scalp cooling market. This expansion was driven by increased awareness of scalp cooling and rapid increase in demand for the device [#6&7]. The biology-driven improvements in the efficacy of the device provided the platform for Paxman to aim for “80:20 efficacy by 2020” and “zero hair loss” long-term [#6]. They also paved the way for a new Safety and Tolerability clinical trial that began in 2019 and aims to provide evidence on whether the new cooling device (that achieves lower scalp temperatures) demonstrates higher efficacy [#6]. If this successfully shows better efficacy, it will be a milestone trial.

Apart from the biological research itself, the research team contributed to the growth achieved by Paxman through ongoing scientific and technical advice based on their extensive testing of the efficacy of cooling for a wide range of chemotherapy agents. Six times a year on average during the assessment period, they provided Paxman with expertise on medical and scientific questions from clinicians, patients and their technical department [#6]. Examples include:

- Writing the preface for Paxman’s Global Clinical Efficacy Brochure in 2019, describing how the biological research allowed Paxman to become the only scalp cooling provider worldwide with a science-based approach to product development (2,500 copies circulated in 25 countries) [#5&6].
- Advice on new drugs and drug combinations and whether scalp cooling would be effective to treat hair loss resulting from treatment with such drugs. In one case, this led to Paxman signing a clinical trial research agreement with one of the world’s leading cancer centres, the Dana-Farber Cancer Institute in Boston, USA [#6d].
- Providing biological evidence for Paxman’s work on other side-effects caused by chemotherapy drugs, such as eyebrow loss and chemotherapy-induced peripheral neuropathy (CIPN; weakness, numbness and pain in hands and feet) [#6d].

- Contribution to Paxman's Global clinical data brochure, providing *"excellent promotional tools to share with our global customer base"* (Paxman) [#5&6d].
- References to the scientific research were also included in the company's patient information [#6].

The researchers have also educated representatives of companies that import the devices into various international markets on the scientific basis of scalp cooling, allowing these key intermediaries to answer important questions from potential end users [#6a&6d]. In 2014, Georgopoulos and Collett became members of Paxman's Scientific Advisory Board. In September 2020, they took part in a webinar which was part of Paxman's worldwide "Conversations with the CEO" series, focusing on the biology of scalp cooling [#10e]. This was attended by >100 delegates from Europe, US and Australia (feedback indicated a great interest in the science that underpins the efficacy of scalp cooling and on developments on combination of cooling with a topical agent). Moreover, Georgopoulos and Collett regularly (twice a year, since April 2019) present an update of their biological work to the UK and US Paxman teams, which allow the team members to understand the biological work and help them 'convey' the biological evidence to relevant professionals in clinics worldwide. Finally, the creation of the Paxman Centre (PSCRC) itself has provided an even stronger platform for the biological research to continue to support Paxman's expansion [#9].

Altogether, Paxman have confirmed the enormous significance of the research and scientific advice provided by Georgopoulos and Collett for their business development, stating that: ***"the support provided... is immeasurable; it has had, and continues to have, significant impact to the work we do around the world. Our relationship with the University has provided us with a sound advisory board which has put the research and know-how behind the commercial decisions we have made"*** [#6d].

Enhancing understanding and knowledge of scalp cooling for clinical professionals:

Paxman have distributed re-prints of the underpinning publications [section 3, Outputs 1,2] at many international conferences during the assessment period, and the researchers presented five posters at two conferences. Steven Jay Isakoff, a medical oncologist at Massachusetts General Hospital Cancer Center, exemplifies the widened acceptance among clinicians of the benefits of scalp cooling as proven by the Huddersfield research: *"Scalp cooling has been a real game changer for so many of our patients with breast cancer...Thanks to the recent expanded FDA indication for the Paxman Scalp Cooling system, so many more patients with solid tumors in the US can now consider this option as a safe and effective way to keep their hair during chemotherapy"* (2018) [#11].

The researchers also reached out directly to oncology nurses, who operate the devices, by assisting the design and facilitating delivery of masterclasses. By the end of 2020, these had been attended by over 70 nurses from 47 different UK Hospitals/Trusts. These classes were very well received, and the very positive feedback (100% of delegates scored it very good or excellent) demonstrates how oncology nurses found them very useful and inspiring [#2]: *"...learning from the scientist and the research that is going on..." "It was good to hear from the speakers that have been involved in the research, published articles on scalp cooling..."*.

Improving quality of life for cancer patients:

According to data collated by Paxman, 98% of NHS Trusts and private providers had acquired Paxman scalp cooling systems by the end of 2020. The introduction of the new device to hospitals improved patient experience and reduced the incidence of alopecia (in 2013 Dutch Registry Data reported in 1,411 patients scalp cooling had a 48% success, but in 2019 a similar study of 7,000 showed 56% efficacy) [#5]. In addition, over the same timeline the number of Paxman systems installed increased from ~1,500 to >3,500 globally, which dramatically increased availability to patient numbers from ~18,000 to >80,000 p.a. [#6]. These developments have made a highly significant impact on patient well-being and quality of life, as testimonials confirm [#1]: *"It was amazing to be able to keep most of my hair. I worked full time throughout my chemotherapy treatment, so being able to keep my hair made me look better than I actually*

felt". "For me it has made a huge difference for my identity through cancer. It has meant that I am comfortable going out in public... I am not stressed about how I look or having to look in the mirror. The difference it has made psychologically is monumental to me".

Moreover, as part of a recent study carried out at Huddersfield University, the impact of scalp cooling on patient wellbeing was quantified through extensive user feedback analysis of >150 patients across 9 countries. 99% of patients who used scalp cooling reported some impact on their emotional wellbeing, with 93% stating a very significant / significant impact on emotional wellbeing in addition to social activities (84%), work activities (77%), relationships with family and friends (70%) and physical / sporting activities (60%) [#12].

Raising awareness and understanding of scalp cooling among the general public:

Drs Georgopoulos and Collett have appeared in Paxman publicity films and featured in national and international press coverage between April 2019 and January 2020, including in the *Daily Mail* (twice) and the *Daily Express* [#10], increasing knowledge and understanding of scalp cooling and the Paxman product. Further publicity followed the creation of the Paxman Research centre (PSCRC) in 2019, including an article in the Clinical Services Journal which advertised the PSCRC worldwide [#9]. A Paxman YouTube video featuring Drs Georgopoulos and Collett explaining the science had been viewed >1,000 times by January 2021 [#10f], in addition to the YouTube video recording from the "Conversations with the CEO" series (above) [#10e].

Awards and nominations:

The researchers' work with Paxman received the prestigious Partnership with Academia award at the Medilink Awards 2016. In 2017, the partnership was shortlisted for the Times Higher Education (THE) Awards in the "Most Innovative Contribution to Business-University Collaboration" category [#8].

5. Sources to corroborate the impact

#1. Patient testimonials <https://coldcap.com/stories/>

#2. Oncology nurse feedback from Paxman Scalp Cooling masterclasses (weblink)

#3. Reference in the Paxman application to the FDA

#4. International Patent Application No. PCT/GB2017/051804 in the name of Paxman Coolers Ltd -- Composition and Apparatus for Treatment of Chemotherapy Induced Alopecia

#5. Global Clinical Efficacy Brochure

#6. a) Letter Paxman Ltd CEO (2019); b) Examples of company interim reports with reference to biological research cited; c) FDA application related letter; d) Cancer patient & chemotherapy treatment-related statistics d) Letter Paxman Ltd CEO (2020)

#7. Paxman Ltd Annual and Interim reports

#8. File providing details of Awards and Nominations, including: a) Shortlisted for Times Higher Education (THE) Award (2017); b) Winner, Medilink Healthcare Award (2016).

#9. Paxman signs agreement with University of Huddersfield (press coverage for the creation of the Paxman Scalp Cooling Research Centre) (2019)

#10. File providing details/links of press coverage, including: a) 27 January 2020: The **Daily Mail** – Health section; b) 10 June 2019: The **Daily Mail** – Health section; c) 12 April 2019: **Daily Express**; d) **Cure Today**, April 2017; e, f) YouTube video links

#11. <https://www.healio.com/news/hematology-oncology/20180611/fda-clears-paxman-scalpcooling-system-for-all-patients-with-solid-tumors>

#12. Study of impact of scalp cooling on patient wellbeing (feedback report to Paxman).