Institution: The University of Manchester

Unit of Assessment: 5 (Biological Sciences)

Title of case study: Improving treatment and prevention of cervical cancer in Kenya

Period when the underpinning research was undertaken: 2003 – 2020

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:
Ian Hampson	Professor in Viral Oncology Reader	2016-present 2003-2016
Lynne Hampson	Reader in Viral Oncology Lecturer	2016-present 2003-2016

Period when the claimed impact occurred: August 2013 – July 2020

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

1. Summary of the impact

Cervical cancer has a high mortality in low/middle income nations, where human papilloma virus (HPV) vaccines are unaffordable, there are no screening programs and limited surgical facilities. University of Manchester (UoM) preclinical research led to a clinical trial in Nairobi repurposing HIV protease inhibitors as a topical, self-applied treatment for HPV-related cervical dysplasia. This showed efficacy against HPV infection and all grades of dysplasia. All women followed up were disease-free one year later. Adoption of clinical practices from this trial, and recommendations from another UoM study on survival of Kenyan women with advanced cervical cancer, has improved disease management in Nairobi by providing: specialist training for healthcare staff; free screening and treatment for ~3,000 women; reduced waiting times.

2. Underpinning research

In 2006 Lynne Hampson (LH) and Ian Hampson (INH) were first to report the off-target activity and mode-of-action of selected HIV protease inhibitors against HPV positive cervical carcinoma cell lines [1]. Lopinavir was identified as the most promising candidate drug and in 2011 LH and INH showed that this compound also activated the interferon induced antiviral protein ribonuclease L in HPV positive cervical carcinoma cells [2]. Furthermore, in collaboration with Professor I Zehbe (Lakehead University, Canada), it was shown that Lopinavir was superior to zinc-finger ejecting compounds as a prospective therapy for HPV related disease [3]. Lopinavir is normally given orally combined with Ritonavir as a treatment for HIV and our work indicated that a higher concentration than could be achieved by oral dosing was needed for anti-HPV activity.

Based on these observations, LH and INH, together with their Kenyan former PhD student Orora Maranga, designed a phase 1 proof-of-concept clinical trial entitled the "Lopinavir as a Topical Treatment" (LOTT) trial for HPV related cervical dysplasia (ISRCTN48776874) which was approved by Kenyatta National Hospital (KNH) ethics board in 2011. Between 2013 and 2014, >800 women attending KNH's Family Planning and Gynaecology Outpatients clinics were screened for HPV and abnormal cytology which resulted in the recruitment of 23 HPV-positive women with high-grade cervical dysplasia. These were treated using a soft-gelatine capsule, oral formulation of the drug Lopimune as a vaginal pessary (generic form of AbbVie's Kaletra – Cipla Ltd). The results, published in 2016, showed that 60% of the 23 treated women returned to normal pathology and 19% regressed to low-grade disease within 3 months [4].

Standard Lopimune capsules consist of a 4:1 *w/w* mixture of Lopinavir and Ritonavir and the outcome was consistent with this mixture having a marked effect as a topical therapy against HPV related cervical dysplasia, supporting the laboratory studies (LH and INH). A patent on this work with LH and INH as inventors [5] was licensed to New Zealand's Douglas Pharmaceuticals and subsequently granted in the USA, Europe and Australia. Since then, LH and INH have been funded by Douglas Pharma to develop an optimised topical formulation of Lopinavir and Ritonavir which has resulted in the filing of two more patents in 2018 (WO2019224780A1 and WO2019224779A1).

LH and INH also carried out a secondary study on the analysis of factors that contribute to the treatment outcome of Kenyan women who have progressed to advanced cervical cancer as a result of having limited access to preventative measures. The majority of these women (~70%) had stage 2B or stage 3 disease and Kaplan Meier plots predicted a 2 year survival of <20% [6]. This is dismal when compared to UK 5 year survival rates for women with stage 2B and 3 disease which are 60-70% and 30-50%, respectively.

3. References to the research

1. **Hampson L**, Kitchener HC, **Hampson IN.** Specific HIV protease inhibitors inhibit the ability of HPV16 E6 to degrade p53 and selectively kill E6-dependent cervical carcinoma cells in vitro. *Antivir Ther* 2006; 11(6):813-825. https://www.intmedpress.com/journals/avt/abstract.cfm?id=543&pid=88
2. Batman G, Oliver AW, Zehbe I, Richard C, **Hampson L, Hampson IN.** Lopinavir up-regulates expression of the antiviral protein ribonuclease L in human papillomavirus-positive cervical carcinoma cells. *Antivir Ther* 2011; 16(4):515-525. https://www.intmedpress.com/journals/avt/article.cfm?id=1786
3. Zehbe I, Richard C, Lee KF, Campbell M, **Hampson L, Hampson IN.** Lopinavir shows greater specificity than zinc finger ejecting compounds as a potential treatment for human papillomavirus-related lesions. *Antiviral Res* 2011; 91(2):161-166. https://doi.org/10.1016/j.antiviral.2011.05.016
4. **Hampson L**, Maranga IO, Masinde MS, Oliver AW, Batman G, He X, Desai M, Okemwa PM, Stringfellow H, Martin-Hirsch P, Mwaniki AM, Gichangi P, **Hampson IN.** A Single-Arm, Proof-Of- Concept Trial of Lopimune (Lopinavir/Ritonavir) as a Treatment for HPV-Related Pre-Invasive Cervical Disease. *PLoS One* 2016; 11(1):e0147917. https://doi.org/10.1371/journal.pone.0147917
5. **Ian Hampson**, **Lynne Hampson**, *Treatment of Cancer and Benign Proliferative Disorders*, Priority Date 23/10/2013: UK (URL WO2015059485A1).
6. Maranga IO, **Hampson L**, Oliver AW, Gamal A, Gichangi P, Opiyo A, Holland CM, **Hampson IN.** Analysis of factors contributing to the low survival of cervical cancer patients undergoing radiotherapy in Kenya. *PLoS One* 2013; 8(10):e78411. https://doi.org/10.1371/journal.pone.0078411

4. Details of the impact

Context

Globally one woman dies from cervical cancer every two minutes, 85% of these deaths in the developing nations. It is caused by infection with high-risk forms of HPV, for which there is no treatment, and uptake of the HPV vaccine is highly variable. In the developed world, the mainstay for preventing cervical cancer is cervical screening and surgical removal of early-stage pre-cancerous lesions. However, in poorer countries screening and treatment facilities are scarce, and even early-stage disease is often treated by full hysterectomy.

Reach and significance of the impact

Health impact – saving lives from cervical cancer

UoM preclinical research [1-3] describing the activity and mode-of-action of the HIV protease inhibitors Lopinavir and Ritonavir against HPV related disease provided the basis for the phase 1 clinical trial of this indication in Kenya [4]. The results were first reported in the Daily Telegraph and on BBC Breakfast TV in 2014 [A], and presented at the Royal Society of Medicine Medical Innovations Summit [B], where the work was noted as "*a truly great achievement*". Long-term follow up of 18 Lopimune-treated women from this trial for >12 months showed complete absence of disease. During the trial, cervical screening identified five women with invasive disease who were referred for immediate hysterectomy, which undoubtedly saved their lives.

The Kenyan trial directly led to Douglas Pharmaceuticals investing GBP4,000,000 [C,D] to fund formulation optimisation and a new proof of concept clinical trial in New Zealand (ACTRN12618001726246p). Initial results, though preliminary, are promising, with three out of the five women enrolled showing remission from high-grade pre-cancerous disease. The study is ongoing pending revisions to the formulation and regimen.

International impact – building capacity and changing clinical practice in Kenya

Kenya has one of the highest incidences of cervical cancer in the world, and poor survival. Although a secondary impact of the basic science research, the trial [4] directly led to changes in clinical practice in Kenya, by providing new equipment and training for Kenyan doctors. This equipment and expertise has been used to establish a continuing programme of free cervical screening and treatment for the poor in Nairobi since 2013.

Furthermore, as a direct result of the Hampsons' research, two registered charities have been established: Cancer Research Trust – Kenya (registered in Kenya in 2012) and Langdales Cancer Trust (registered in England in 2016), with INH and LH as Trustees. The charities have screened and/or treated approximately 3,000 women to date [E], including over 1,000 with advanced cervical cancer. In addition, The Janice Cholerton Cancer Hospital (JCCH) in Nairobi, recognised as a centre of excellence, was established by Kenneth Cholerton in 2017 as a direct result of the Hampsons' research, and has screened or treated more than 2,400 women for pre-cancer to date [F].

Recommendations from the Hampsons' study on factors affecting the survival of Kenyan women undergoing treatment for advanced cervical cancer [6] have also directly informed changes in the clinical management of gynaecological cancer patients in Nairobi, with the following benefits [E]:

- Management of **all** gynaecological cancer patients in Kenyatta National Hospital (KNH), has been changed by creating the 'Gynaecologic Oncology Unit' with 11 specialists (previously these patients were managed by any general gynaecologist). This has reduced waiting times and resulted in better patient treatment outcomes due to timely interventions:
    - 4 months to 3 weeks from diagnosis of operable cervical cancer to theatre.
    - 8 to 2 weeks for examination under anaesthesia for staging and biopsy.
    - 12 to 3 weeks at the colposcopy clinic.
    - >8 to ~1 month between diagnosis and commencement of radiotherapy, due to enhanced radiotherapy infrastructure.
- A one-stop 'See and Treat' approach has been introduced in the cervical cancer screening clinic.
- KNH trains residents and nurses (70 to date) in the screening and treatment of cervical lesions. A two-year post-graduate fellowship program in Gynaecologic Oncology has also been developed (first intake of 8 fellows will graduate in late 2020).
- Standardised algorithms and operating procedures on management of abnormal cervical smears (recommended in [6]), have been produced and disseminated to staff, residents

and nurses, and freely shared with other Kenyan hospitals. Importantly they take into account infrastructural and financial constraints, and have influenced management of gynaecologic cancers at a national level, via Orora Maranga's role as Chair of the Ministry of Health Technical Working Group for this area since 2017.

In summary, Kenneth Cholerton said: "*There is no doubt that the research conducted by Ian and Lynne Hampson at the University of Manchester has played a crucial role in what has been achieved in Kenya to date*" [F].

Policy impact – informing political debate

The use of drug repurposing in the Kenyan trial was also the reason for LH's and INH's invitation to the House of Lords to take part in the Medical Innovation Bill (informally called the Saatchi Bill) debate in 2014 [G]. The Bill's aim was to permit doctors to use unconventional treatments in certain circumstances. After modifications, this resulted in The Access to Medical Treatments Bill passing into law in 2016.

5. Sources to corroborate the impact

A. Daily Telegraph 'End in sight for cervical cancer?' (16 Feb 2014); BBC Breakfast TV appearance by Ian and Lynne Hampson 'New use for the HIV drug Lopinavir as a treatment for early stage cervical cancer' (aired 5 Dec 2014).

B. Medical Innovations Summit at the Royal Society of Medicine (5 April 2014), where the Hampsons' research was noted as "a truly great achievement".

C. Letter from Chief Scientific Officer, Douglas Pharmaceuticals (9 July 2020), confirming investment in clinical trials as a direct result of the Hampsons' research.

D. National Business Review, 'Douglas signs new cancer drug R&D deal with Manchester University' (1 February 2017).

E. Letter from Former Assistant Director and Former Head of Department of Obstetrics & Gynaecology, Kenyatta National Hospital, Nairobi, Kenya (30 May 2020) – confirming the role of the Hampsons' research in informing the changes in management of gynaecological cancer patients at the hospital.

F. Letter from Kenneth Heathcote Cholerton (24 May 2020), philanthropist and former medical research charity Honorary Chairman, confirming the key role of the Hampsons' research in changing clinical practice in Nairobi, and in the establishment of the Janice Cholerton Medical & Cancer Hospital.

G. Medical Innovation Bill (Saatchi Bill) debate, streamed live from the House of Lords, 24 February 2014 (555 views). INH's contribution is at 31.12 minutes. This led to The Access to Medical Treatments Bill passing into law in 2016.