Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Development of an Effective Cure for River Blindness (Onchocerciasis) and Elephantiasis (Lymphatic Filariasis) and a new Tool for Control, Elimination and Morbidity Management.

1. Summary of the impact

Scientists at the Liverpool School of Tropical Medicine (LSTM) have proven that targeting an essential bacterial symbiont, *Wolbachia*, with a course of antibiotics cures patients of their parasitic worms and improves disease pathology. This discovery in 1999 offers superior efficacy compared to existing anti-filarial drugs delivering prophylaxis, transmission blocking, safe macrofilaricidal activity and improved case management therapy. This approach has been endorsed by WHO elimination programmes for onchocerciasis, (Onchocerciasis Elimination Programme for the Americas, OEPA) and lymphatic filariasis (Global Programme to Eliminate Lymphatic Filariasis, GPELF). The Centre for Disease Control (CDC), also recommends this new strategy for elimination and morbidity management.

2. Underpinning research

Professor Mark Taylor established the research at LSTM in 1993 and was assisted by Dr Joseph Turner (Lecturer, 2010-), Dr Louise Ford (PDRA, 2007-) Dr Darren Cook (PDRA, 2005-), Dr Denis Voronin, (PDRA. 2009-), Dr Kelly Johnston (PDRA, 2005-) and Dr Helen McGarry (PDRA, 2003-2008) to study the filarial parasites which cause elephantiasis (*Wuchereria bancrofti* and *Brugia malayi*) and river blindness (*Onchocerca volvulus*). Both of these diseases are part of a recent focus on neglected tropical diseases (NTDs), recognizing that about a billion more people are at risk and millions are infected with NTDs.

Professor Taylor has made significant progress discovering a previously unexpected role of *Wolbachia* bacterial symbionts as drivers of filarial disease, essential contributors to the biology of filarial nematodes, and as a target for treatment through antibiotic therapy. He has shown that the antibiotic doxycycline can be used to treat patients with fewer adverse effects than existing therapies such as ivermectin. New drugs are still needed to reduce the treatment course and are being developed in partnership with industry. The breakthrough stimulated the formation of the 'Anti-Wolbachia' (A·WOL I) consortium in 2007 and A·WOL II in 2013, to search for new drugs active against *Wolbachia*. The consortium, led by Taylor, consists of internationally recognised researchers in the UK, Germany, Africa and USA and collaborates with pharmaceutical companies.

Professor Taylor's group undertook ten randomised and placebo controlled phase II field trials using doxycycline as a novel treatment against lymphatic filariasis and onchocerciasis. Field trials were conducted in collaboration with A·WOL consortium members in Germany and Africa, with the group at LSTM contributing to the planning, protocol design, ethics, management and data analysis. A course of doxycycline that depletes the bacterial endosymbionts, leads to prolonged reduction in microfilaraemia and the death of adult worms (78-92% cure rate) with avoidance of adverse events to treatment experienced with standard anti-filarial treatments, due to either target species or to co-infections with *Loa loa*. In individuals with disease, a course of treatment can even bring about an improvement in the pathology of lymphodema and hydrocele (swollen fluid filled scrotal sac) an effect which is retained in patients without active infection [1,2,3].

The new anti-wolbachial therapy provides an alternative to the treatment for onchocerciasis and lymphatic filariasis in areas co-endemic with loiasis. Previous anti-macrofilarial treatments have resulted in the rapid kill of *L. loa* microfilariae but at the risk of severe complications resulting in encephalopathy, coma and death. However, by using antibacterial drugs these severe adverse events are avoided because *L. loa* microfilariae do not have *Wolbachia* symbionts. This has potential to overcome a major barrier to the implementation of mass drug administration (MDA) programmes.

Findings by A·WOL of 6 and 8 week courses of doxycycline have been reported as a safe and well

tolerated treatment for lymphatic filariasis with significant activity against adult worms and microfilaraemia [4], treatment improves mild to moderate lymphodema independent of on-going infection. This benefit expands to the entire population of patients suffering from lymphodema. Doxycycline is able to kill the adult worms, making doxycycline the first drug already approved for human use that controls the parasite and the quality of life of persons with pathology [2].

To test whether a 6-week course of treatment was deliverable through community-directed MDA approaches, in 2007 a community trial of treatment with doxycycline was carried out in two health districts in Cameroon, co-endemic for *O. volvulus* and *L. loa*. With 17,519 eligible subjects, the therapeutic coverage was 73.8% with 97.5% compliance, encouraging the feasibility of using doxycycline community-directed delivery in restricted populations of this size. The evaluation of the effectiveness of this delivery of doxycycline showed significant improvements over standard strategies, even up to four years after delivery, which is not dependent upon co-administration of ivermectin [4, 5]. These findings show that a multi-week course of treatment is not a barrier to community-delivery of MDA in restricted populations of this size and supports its implementation to complement existing control strategies for onchocerciasis [6].

3. References to the research

1. **Taylor MJ**, **Makunde WH**, **McGarry HF**, **Turner JD**, Mand S, Hoerauf A. Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti: a double-blind, randomised placebo-controlled trial.* (2005) The Lancet, Volume 365, Issue 9477, Published: 18–24 June 2005, Pages 2116–2121 Citations: 112 Impact Factor: 23.878

2. Debrah AY, Mand S, Specht S, Marfo-Debrekyei Y, Batsa L, Pfarr K, Larbi J, Lawson B, **Taylor M**, Adjei O, Hoerauf A. 'Doxycycline reduces plasma VEGF-C/sVEGFR-3 and improves pathology in lymphatic filariasis'. (2006) PLoS Pathogens, Vol 2, Issue 9, 0829-0843. Citations: 31 Impact Factor: 6.056

3. Debrah AY, Mand S, Marfo-Debrekyei Y, Batsa L, Pfarr K, Lawson B, **Taylor MJ**, Adjei O, Hoerauf A. Reduction in levels of plasma vascular endothelial growth factor-A and improvement in hydrocele patients by targeting endosymbiotic Wolbachia sp. in *Wuchereria bancrofti* with doxycycline. (2009) Am J Trop Med Hyg. 80(6): 956-63. Citations: 23 Impact Factor: 2.795

4. Mand S, Debrah AY, Klarmann U, Batsa L, Marfo-Debrekyei Y, Kwarteng A, Specht S, Belda-Domene A, Fimmers R, **Taylor M**, Adjei O, Hoerauf A. Doxycycline improves filarial lymphedema independent of active filarial infection: a randomized controlled trial. (2012) Clinical Infectious Disease. 55(5):621-30. Citations: 3 Impact Factor: 9.374

5. **Turner JD**, Tendongfor N, Esum M, **Johnston KL**, **Langley RS**, **Ford L**, **Faragher B**, Specht S, Mand S, Hoerauf A, Enyong P, Wanji S, **Taylor MJ**. Macrofilaricidal Activity after Doxycycline Only Treatment of *Onchocerca volvulus* in an Area of *Loa loa* Co-Endemicity: A Randomized Controlled Trial. (2010) PLOS Neglected Tropical Diseases Volume: 4 Issue: 4 Article Number: e660 Published: APR 2010 Citations: 29 Impact Factor: 4.752

6. **Tamarozzi F**, Tendongfor N, Enyong PA, Esum M, Faragher B, Wanji S, **Taylor MJ**. Long term impact of large scale community-directed delivery of doxycycline for the treatment of onchocerciasis. (2012) Parasites & Vectors. 2012 5:53. Citations: 7 Impact Factor: 3.246

Key Research Grants

2007–2012, **Bill & Melinda Gates Foundation**, 'Anti-Symbiotic Treatment of Filariasis' (A-WOL I), $23m, **Mark Taylor** (PI).

2013-2016, **Bill & Melinda Gates Foundation**, 'A-WOL II Macrofilaricidal Drug Discovery', $5m, **Steve Ward** (PI, LSTM Deputy Director)

2013-2015, **Bill & Melinda Gates Foundation**, 'A·WOL II: Macrofilaricidal Drug

Development' $4m, **Mark Taylor** (PI)

2013-2018, **DFID** 'Phase III trial for community doxycycline in efficient vector transmission hotspots' £1m,**Centre for Neglected Tropical Diseases (CNTD), LSTM**

4. Details of the impact

Policy Impact

LSTM research findings changed WHO and the CDC strategies, treatment guidelines and recommendations. In 2012 the WHO OEPA adopted doxycycline for the treatment of residual cases in the North-Eastern focus in Venezuela. Attention to operational elements of the river blindness programme in the Americas is highly necessary in order to achieve and maintain the elimination of transmission. The geographically hard to reach location of the affected area coupled with the migratory nature of the population make it especially difficult to maintain regular treatments. OEPA refers to the use of an alternate antibiotic doxycycline as ensuring full elimination of infection and transmission [7].

The WHO GPELF endorsed the use of doxycycline as a new tool for morbidity management of elephantiasis in 2012. The Global Task Force for Health's 2012 monitoring and evaluation working group on disease specific indicators, endorsed the use of doxycycline (6 weeks) for individual treatment of adults as an alternative, [8, page 6]. It also refers to the use of doxycycline for adults (200 mg/day) for 6 weeks as an alternative and two LSTM studies [4,6]. The sixth meeting of the WHO Strategic and Technical Advisory Group for NTD's also states "for clinical cases, any of the following regimens have been proposed and may be considered, for adults, doxycycline (200 mg/day) for 6 weeks is under consideration as an alternative" [9].

The WHO report from the 2009 Inter-American Conference on Onchocerciasis concluded that "progress towards eliminating river blindness in the region of the Americas" and noted that a 6-week course of daily oral doxycycline has been shown to kill adult *O. volvulus* worms. Doxycycline kills endosymbiotic bacteria (*Wolbachia*) that provide important nutritional requirements to the worms; without the bacteria the worms become sterile and slowly die. The conference recommended that national programmes consider providing doxycycline treatment (but necessarily exclude young children and pregnant women) on a selective basis [10].

CDC recommends doxycycline treatment options for onchocerciasis [11] and lymphatic filariasis [12] to health professionals. One objective of the A·WOL programme is to promote advocacy of A·WOL's outcomes by interfacing with CNTD and external scientific advisors to facilitate dialogue, representation and engagement with control programmes: the African Programme for Onchocerciasis Control (APOC), OEPA and GPELF, stakeholder meetings and NTD community forums. The membership of the A·WOL Consortium and the External Scientific Advisory Committee (ESAC) in particular is ideally equipped through its excellent networks to promote the findings and practical opportunities the A·WOL project provides.

The A·WOL ESAC includes key stakeholder members from APOC, OEPA, GPELF, the Mectizan Donation Program [13], Drugs for Neglected Diseases initiative (DNDi) and NTD Global Health experts [14] (Prof David Molyneux-former LSTM). In addition, the publication of A·WOL research findings in both high impact journals and at international conferences and meetings is an ongoing process which adds to the evidence base in order to advocate for the implementation of an anti-*Wolbachia* based approach for filariasis therapy.

CDC Recommended Treatment regime for *Onchocerca volvulus*- based on LSTM research

Usage/Drug	**Adult Dose**	**Pediatric dose**
To kill microfilariae: ivermectin	150 mcg/kg orally in one dose every 6 months	150 mcg/kg orally in one dose every 6 months
To kill macrofilariae: doxycycline	200 mg orally daily for 6 weeks	200 mg orally daily for 6 weeks

Commercial Impact

The breakthrough of anti-wolbachial therapy stimulated the creation of both product discovery and development pipelines at LSTM to identify new antibiotics which target *Wolbachia* and could be used to combat elephantiasis and river blindness.

Since 2007, LSTM has been working with industrial partners through A·WOL collaborations [15] with CombinatoRx, Forma Therapeutics, Paratek, Inventa Technologies (S) Pte Ltd, Anacor Pharmaceuticals Inc, Abbott/AbbVie, Pfizer Inc, Bio-focus DPI Ltd, SIMM (Shanghai Institute of Materia Medica), AstraZeneca, Dupont, Broad Institute, MMV, DNDi, and TB Alliance plus others to discover and develop drugs that work to clear the *Wolbachia* symbiont, but can do so in a treatment course of 7 days or less and be safe for children and in pregnancy – where a 4-6 week course of doxycycline cannot be given.

LSTM research led, in 2013, to both the A·WOL Macrofilaricide Drug Discovery project, progressing six new chemical series towards pre-clinical candidate selection, and the A·WOL Macrofilaricide Drug Development project, taking the best registered and re-purposed drugs from LSTM's screening campaign to optimise the best combination of drugs for MDA programmes. Both A·WOL programs include collaboration with pharmaceutical companies providing industrial investment to cover the entire drug discovery and development process.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

7. Contact: Director, Onchocerciasis Elimination Program for the Americas (OEPA). Confirming they have adopted doxycycline for the treatment of residual cases in the North-Eastern focus in Venezuela.

8. WHO Global programme to eliminate LF meeting report http://apps.who.int/iris/bitstream/10665/78611/1/WHO_HTM_NTD_PCT_2013.5_eng.pdf

9. WHO Report of the sixth meeting of the WHO strategic and Technical Advisory Group for NTD. http://www.who.int/neglected_diseases/sixth_stag/en/index.html

10. Report from the 2009 InterAmerican Conference on Onchocerciasis: progress towards eliminating river blindness in the Region of the Americas http://www.who.int/wer/2010/wer8533.pdf

11. Centers for Disease control recommends treatment options for onchocerciasis http://www.cdc.gov/parasites/onchocerciasis/health_professionals/index.html

12. Centers for Disease Control recommends treatment options for lymphatic filariasis http://www.cdc.gov/parasites/lymphaticfilariasis/treatment.html

13. Contact: Director of the Mectizan Donation Program. Confirming debate has been stimulated and informed by research evidence.

14. Contact: Director of the River Blindness Program, Lymphatic Filariasis Program, confirming debate stimulation and implementation has been and informed by research evidence.

15. Collaborative agreements with industry can be provided on request.