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| Institution: University of the West of Scotland | | |
| Unit of Assessment: 3: Allied Health, Dentistry Nursing and Pharmacy | | |
| Title of case study: New effective prevention and treatment pathways for devastating eye condition, <i>Acanthamoeba</i> keratitis | | |
| Period when the underpinning research was undertaken: 2006 - 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: |
| Fiona Henriquez | Professor | 2005 - 2020 |
| Roderick Williams | Lecturer | 2013 - 2020 |
| William G. MacKay | Reader | 2012 - 2020 |
| Period when the claimed impact occurred: 2016 - 2020 | | |
| Is this case study continued from a case study submitted in 2014? No | | |
| 1. Summary of the impact | | |
| <p>The team has discovered effective prevention and treatment for the serious eye condition <i>Acanthamoeba</i> keratitis (AK), which affects millions of people globally. In ground-breaking research, UWS has determined that the anti-fungal compound voriconazole can be used for AK, demonstrating curing in the Royal Victoria Infirmary in Newcastle. Our expertise has facilitated a clinical-academic-patient network to inform best practice, diagnosis and early treatment of the condition, resulting in a reduction in the number of people with AK in Scotland. Our award-nominated research has resulted in increased knowledge exchange and awareness of AK across world-leading healthcare and pharmaceutical networks. Experts from Bausch and Lomb based in the USA, one of the world's largest eye care products, have engaged with the UWS team and cited the research for changing the industry attitudes towards AK.</p> | | |
| 2. Underpinning Research | | |
| <p><i>Acanthamoeba</i> keratitis (AK) is particularly prevalent amongst contact lens users. Contact lens users are at risk of contracting the devastating condition. Affecting 1,200,000 to 3,000,000 people each year, AK is described by many patients as a life-altering and devastating condition that can lead to blindness and removal of the affected eye.</p> <p>There are several factors in the challenge in finding new treatments for AK. Firstly, current drug regimens require administration to the eye of the patient as part of a gruelling regime, often toxic to humans and ineffective in ridding the patient of AK, due to the microbe's adaptability and resistance to drugs. Unfortunately, it is an infection that falls under the radar of big pharma, but our work with healthcare and pharmaceutical networks across the globe is raising its profile. To address this the team characterised existing medicines meant for other conditions, with the view of repurposing them for AK. This is a considerably more attractive commercial approach for the pharmaceutical industry to address a rare disease.</p> <p>The research is underpinned by university, charity and industry grants, and due to its importance and success at investigating the understudied pathogen, the University has contributed to 3 additional UWS studentships, and a Carnegie Trust PhD studentship has also been won.</p> <p>We have investigated how <i>Acanthamoeba</i> interacts with human immune cells [3.1] and commenced a programme of research to enable the identification of inhibitors that are non-toxic to humans, but that target essential pathways to <i>Acanthamoeba</i>. Also, it is important that any anti-acanthamoebic drug, does not cause this pathogen to transform into cysts. Cysts are resistant to current treatments and biocides, thus creating the ultimate challenge to clearing infection from a patient. Thus far, we have characterised three metabolic pathways [3.2-3.5] and membrane disruption [3.6]. From these studies, it emerged that <i>Acanthamoeba</i> has unique gene structures with evidence of new gene fusions that indicate novel evolutionary processes and that pathways can be therapeutic targets.</p> | | |

Impact case study (REF3)

Specifically, we have built upon our knowledge of *Acanthamoeba* biochemistry to prove that the established commercial anti-fungal, Voriconazole can kill *Acanthamoeba* [3.4]. Also, we have characterised other essential amino acid pathways and cell membrane structures present in *Acanthamoeba*, but not humans, for rational drug design [3.5,3.6]. Importantly, these studies reveal that we can kill *Acanthamoeba* and not allow them to transform into cysts. We have also characterised compounds that kill cysts [3.6].

Leading corneal surgeon from the NHS, Sathish Srinivasan, actively requested to become part of the team in 2018, as he identified its huge potential to lead to effective treatment of *Acanthamoeba* and inform the millions of contact lens users worldwide of the dangers. He became a visiting Professor to UWS in October 2018.

This research has also informed interdisciplinary research projects, including understanding the biology of *Neoparamoeba perurans*, the causative agent of amoebic gill disease in salmon aquaculture (impact case study UOA7).

Our research has been recognised via a nomination for the Queen's Anniversary Prize, as well as being shortlisted for Research Project of the Year at The Herald's Higher Education Awards in 2019.

3. References to the research

3.1 Mattana, A., Sanna, M., Cano, A., Delogu, G., Erre, G., Roberts, CW., **Henriquez, FL.**, Fiori, PL., Cappuccinelli, P. (2016) 'Acanthamoeba castellanii Genotype T4 Stimulates the Production of Interleukin-10 as Well as Proinflammatory Cytokines in THP-1 Cells, Human Peripheral Blood Mononuclear Cells, and Human Monocyte-Derived Macrophages', *Infection and Immunity*, 84(10):2953-2962. <https://doi.org/10.1128/iai.00345-16>.

3.2 Maguire, F., **Henriquez, FL.**, Leonard, G., Dacks, JB., Brown, MW., Richards, TA. (2014) 'Complex patterns of gene fission in the eukaryotic folate biosynthesis pathway', *Genome Biology and Evolution*, 6(10):2709-2720. <https://doi.org/10.1093/gbe/evu213>.

3.3 Henriquez, FL., Campbell, SJ., Sundararaj, BK., Cano, A., Muench, SP., Roberts CW (2015) 'The Acanthamoeba shikimate pathway has a unique molecular arrangement and is essential for aromatic amino acid biosynthesis', *Protist*, 166(1): 93-105. <https://doi.org/10.1016/j.protis.2014.12.001>.

3.4 Thomson, S., Rice, CA., Zhang, T., Edrada-Ebel, R., **Henriquez, FL.**, Roberts, CW., (2017) 'Characterisation of sterol biosynthesis and validation of 14 α -demethylase as a drug target in Acanthamoeba', *Scientific Reports*, 7:8247. <https://doi.org/10.1038/s41598-017-07495-z>.

3.5 Rice, CA., Campbell, SJ., Bisson, C., Owen, HJ., Sedelnikova, SE., Baker., PJ, Rice, DW., **Henriquez, FL.**, Roberts, CW., (2018) 'Structural and functional studies of histidine biosynthesis in Acanthamoeba spp. demonstrates a novel molecular arrangement and target for antimicrobials', *PLoS One*, 13(7):e0198827. <https://doi.org/10.1371/journal.pone.0198827>.

3.6 Mooney, R., Masala, M., Martia, I T., McGinness, C., **Henriquez, FL.**, Williams, RAM., (2020) 'Alkyl-carbon chain length of two distinct compounds and derivatives are key determinants of their anti-Acanthamoeba activities', *Scientific Reports*, 10(1):6420. <https://doi.org/10.1038/s41598-020-62934-8>.

Grants

3.A Henriquez, FL., *Biocide Testing Against Acanthamoeba: BluTest Laboratories Ltd*, Scottish Funding Council, Jan 2011 to Apr 2011, GBP5,000.00

4. Details of the impact

The impact of UWS AK research is diverse, and it has been achieved through the integration of research with stakeholders and beneficiaries in the areas of clinical practice in the UK, patient advocacy worldwide, eye-care industry in the USA and professional development in the UK.

Impact on clinical approach

Following a **Medical Contact Lens and Ocular Surface Association** meeting in November 2016, we were approached by an Ophthalmologist from the **Royal Victoria Infirmary in Newcastle**, requesting our support in the diagnosis and subsequent medication of a patient, whose keratitis infection had deteriorated. We received a sample of the cornea, on which we performed cultures – following our culture protocols – developed at UWS. The team advised the use of voriconazole as a treatment for the patient based on research [3.4], and in May 2017, the Ophthalmologist advised the team, patient was healing. He wrote: *'I have reviewed the patient this morning and her epithelium is healed. She started Voriconazole a month ago and is now using it q.d.s.'* This highlights that the team's research-based treatment protocol was used effectively, the patient's epithelium healed and the eyesight was saved [5.1].

Our expertise in culture methodology, described in our research publications, allowed UWS to introduce state-of-the-art practice through academic clinical partnership with early diagnostic and treatment protocols for AK (**NHS Ayrshire and Arran** through the visiting Professor, and **Greater Glasgow and Clyde**). One challenge in AK diagnosis is that many biopsies are culture-negative, meaning that *Acanthamoeba* cannot be isolated and cultured easily from corneal scrapes and biopsies. However, our pioneering research has recently led to the team to receive human corneal biopsies from AK patients at **Gartnavel Hospital** in order to characterise the *Acanthamoeba* isolates and test drug efficacy on each isolate. This contributes to an emerging AK isolate biobank in collaboration with the healthcare large corporation **Bausch and Lomb in the USA** and Ophthalmologists from **UK, USA, Italy, and Canada**, and in research partnership with the **London School of Hygiene and Tropical Medicine** and the **University of New South Wales, Australia**.

Impact on supporting patients to raise awareness and speak about their experiences

The *Acanthamoeba* keratitis **Patient Advocate and Founder & Administrator [5.2]** states: *'the impact of the research performed at UWS, focused on Acanthamoeba keratitis has enabled many patients (alias AK Warriors, a group of over 1,500 members from around the world, who have come together through social media) to further understand what Acanthamoeba is and how, this eye infection, causes infection in the cornea'*. Understanding AK from the patients' point of view is critical to designing effective research. Through patient groups (participation in 8th AK patient meeting London 5th March 2020), we know that patients have many questions: *'why do medicines not work?'; 'how did I get AK?'; 'why was I misdiagnosed?'*. The knowledge acquired through our AK drug development research has provided a critical understanding of why treatments are so incredibly difficult and why they can fail. The team has supported two students in England who have developed an innovative way to **raise awareness of the disease through film**. UWS research has been cited and involved in both films [5.3, 5.4]. We also support and contribute regularly to the AK awareness information network set up to increase awareness of AK and help people understand the infection they are living with [5.5, 5.6].

Impact on professional practice

Our research has already been widely reported in professional magazines [5.7] and presented at professional conferences and local societies (attendees included local optometrists). This has led to a reduction of cases in the West of Scotland – from 17 in 2014 to 5 in 2020 (data from Gartnavel Hospital), linked to a change in referral practice with earlier identification. The consultant Ophthalmologist at Gartnavel Hospital [5.8] wrote: *'I constantly take referrals from community optometrists and I can confirm there is certainly a heighten awareness of acanthamoeba infection among the community optometrists. The referrals come from them at very early stages of the disease, which makes a big difference. My opinion, your work with the optometrist has contributed to the heighten awareness and early referrals and benefited all.'*

Impact on industry

An invited presentation to the **British Contact Lens Association (BCLA)** 2019 workshop 'Acanthamoeba keratitis, from the lab to the eye', with a task to present our research and challenges we had identified in the diagnosis and management of AK has led to a globally-significant industry engagement. **A Senior Research Scientist at Bausch and Lomb**, based in the USA - one of the world's largest suppliers of eye care products - quotes [5.10] that '*this research is changing attitudes towards this infection within industry*' and verbally that '*we [the company] are engaged with research undertaken at UWS, in the context of ensuring that their products are effective against AK*'. This is further evidenced by confidentiality agreement between UWS and Bausch and Lomb, allowing UWS researchers to showcase how compounds of eye-care products can influence AK diagnosis and treatments. Our pioneering research described in [3.6] was thus patented [5.9] with the intent to inform industry of the important requirement of eye-care solutions, including contact lens solutions, to be able to kill *Acanthamoeba* and importantly, its cyst stage.

5. Sources to corroborate the impact**Impact on clinical approach**

5.1 Testimonial from Ophthalmologist treating the patient Royal Victoria Infirmary, Department of Ophthalmology, Newcastle, who recovered from AK after being treated with voriconazole, characterised through the research published in [3.5].

Impact on supporting patients

5.2 Testimonial from an Acanthamoeba Keratitis Patient Advocate and Founder & Administrator of www.acanthamoebakeratitis.info

5.3 Documentary by an AK sufferer, including interview with Professor Fiona Henriquez <https://www.youtube.com/watch?v=VsyAGrQ6WzQ>

5.4 Documentary by an AK sufferer, where UWS team has been credited for supporting this endeavour <https://drive.google.com/file/d/1s2ytJC1mdZAOMYxITY7YeolFlo8GdsTj/view>

5.5 Good Morning Britain / Stv News Report <https://news.stv.tv/west-central/treatment-discovery-for-serious-rare-eye-condition?top>

5.6 Radio Interviews <https://audioboom.com/posts/7336890-a-sight-robbing-parasite-that-lurks-in-your-water> and <https://audioboom.com/posts/7527140-protect-your-contact-lenses-from-a-dangerous-eye-parasite>

Impact of professional practice

5.7 <https://www.eyenews.uk.com/features/ophthalmology/post/new-solutions-in-the-prevention-and-treatment-of-acanthamoeba-keratitis>

5.8 Testimonial from the Consultant Ophthalmologist and Corneal specialist, Gartnavel Hospital, Glasgow

Impact on industry

5.9 Patent protecting research and result that have been published in [3.6] WO/2021/028696 AMOEBICIDAL COMPOSITIONS FOR CONTACT LENS SOLUTIONS Mooney, Ronnie, Henriquez, Fiona, Williams, Roderick

5.10 Testimonial from the Senior Research Scientist at Bausch and Lomb Testimonial from the Senior Research Scientist at Bausch and Lomb