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| **Institution:** University of Dundee | | |
| **Unit of Assessment:** UoA 5 Biological Sciences | | |
| **Title of case study:** Invention and deployment of single dose cure and chemoprotective agent for malaria | | |
| **Period when the underpinning research was undertaken:** 2009-present | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):**<br><br>1. Dr. Beatriz Baragaña<br>2. Prof. Ian Gilbert<br>3. Prof David Gray<br>4. Prof. Alan Fairlamb CBE<br>5. Prof. Kevin Read<br>6. Prof. Paul Wyatt | **Role(s) (e.g. job title):**<br><br>1. Apicomplexan Portfolio Manager, Drug Discovery Unit (DDU)<br>2. Head of the Division of Biological Chemistry and Drug Discovery<br>3. Head of Biology, DDU<br>4. Professor of Biochemistry<br>5. Head of Drug Metabolism and Pharmacokinetics, DDU<br>6. Director of the Wellcome Centre for Anti-Infectives Research and Head of the Drug Discovery Unit | **Period(s) employed by submitting HEI:**<br>1. 2007-present<br>2. 2005-present<br>3. 2010-present<br>4. 1996-present<br>5. 2008-present<br>6. 2006-present |
| **Period when the claimed impact occurred:** 2013-present | | |
| **Is this case study continued from a case study submitted in 2014?** N | | |

## 1. Summary of the impact

Malaria kills 400,000 people annually, the majority being children. Resistance to current treatments has generated an urgent need for new drugs effective across different parasite life-cycle stages, to enable malaria treatment and eradication. Research at the University of Dundee's Drug Discovery Unit has resulted in the invention of a novel small molecule with demonstrated ability to cure malaria, prevent infection, and block transmission with a single dose. This research:

- de-risked pre-clinical drug discovery, incentivising partnership between Medicines for Malaria Venture and Merck for clinical development of the Dundee molecule;
- led to a successful first-in-human clinical trial with accelerated volunteer infection study;
- uncovered a novel mode of action, unblocking the pipeline for crucial combination treatments to combat malaria.

## 2. Underpinning research

Malaria is a debilitating parasitic disease posing a risk to nearly half the world's population. The WHO estimated 229 million cases of malaria in 2018, with 409,000 deaths, most in young children and pregnant women in sub-Saharan Africa. Disruption of malaria treatment services due to COVID-19 is likely to increase malaria deaths in 2020. The predominant malaria parasite, *Plasmodium falciparum*, has developed resistance to many drugs, including the core artemisinin component of current first-line therapies. New drugs are urgently needed to effectively treat and eventually eradicate malaria. New anti-malarials must meet several requirements: (a) novel modes of action with no cross-resistance to current drugs; (b) single-dose treatments with activity against blood-stage disease; (c) activity against liver stages that can prevent disease development (chemoprotection or prophylaxis); (d) compounds active against the sexual stages (gametocytes) to prevent transmission of malaria. DDD107498, invented by researchers in the Drug Discovery Unit (DDU) at the University of Dundee, has a completely novel mode of action

and meets all these criteria. It is one of only three compounds with this profile undergoing clinical development by the Medicines for Malaria Venture (MMV) not-for-profit public-private R&D partnership.

Invention of DDD107498 began by screening a Dundee in-house chemical compound library **[R1]** to identify compounds that inhibited growth of *P. falciparum* in human red blood cells. The screening tested 4,731 compounds and succeeded in identifying a promising compound series **[R2]**. A subsequent DDU medicinal chemistry programme optimized properties of the compound series through iterative cycles of designing improvements, making the improved compounds, and biological testing of their potency and metabolic stability **[R3]**. Further rounds of the design-make-test cycle improved their oral bioavailability, permeability, potency and selectivity. This remarkable chemical evolution transformed a series with suboptimal properties into a pre-clinical candidate with approximately 100-fold increase in potency and much improved chemical properties **[R4]**. The final compound was active against drug-resistant parasites with no cross-resistance to current antimalarial drugs. It had remarkable potency, oral bioavailability and a long half-life in malaria mouse models across multiple life cycle stages; cured blood stream infection; had crucial transmission-blocking activity; and could even prevent infection in the first place **[R3, R4]**.

The DDU, together with collaborators, identified that the compound acted through inhibition of protein synthesis, with parasite translation elongation factor eEF2 as its target **[R4]**. After treatment with DDD107498 and consequent inhibition of eEF2, the parasites cannot make essential proteins, and die. This discovery confirmed DDD107498's completely novel mode of action, one that parasites will not have had a chance to develop resistance to, making it a very attractive prospect for further development. This work, published in *Nature* in 2015, is highly cited and received significant media coverage **[R4]**. A patent was filed around the compound series **[R5]**.

This huge success in going from fundamental discovery science to a drug in successful clinical trial, highlights the unique on-going capability and impact of the DDU in translating world-class discovery research into new de-risked targets and candidate drugs. Its continuing malaria drug discovery effort has now identified a second compound series with a novel mode of action that has provided additional molecules to the malaria drug discovery pipeline.

## 3. References to the research (indicative maximum of six references)

**[R1] Brenk, R, Schipani, A, James, D, Krasowski, A, Gilbert, IH**, **Frearson, J** & **Wyatt, PG** (2008) 'Lessons learnt from assembling screening libraries for drug discovery for neglected diseases', *ChemMedChem.*, vol. 3, no. 3, pp. 435-444. DOI: 10.1002/cmdc.200700139

**[R2] Hallyburton, I**, **Grimaldi, R, Woodland, A**, **Baragana, B, Luksch, T, Spinks, D, James, D**, Leroy, D, Waterson, D, **Fairlamb, AH**, **Wyatt, PG**, **Gilbert, IH & Frearson, JA** (2017) 'Screening a protein kinase inhibitor library against *Plasmodium falciparum*', *Malaria Journal*, vol. 16, 446, pp. 1-11. DOI: 10.1186/s12936-017-2085-4

**[R3] Baragaña, B**, **Norcross, NR, Wilson, C, Porzelle, A, Hallyburton, I, Grimaldi, R, Osuna-Cabello, M, Norval, S, Riley, J, Stojanovski, L, Simeons, FRC**, **Wyatt, PG**, Delves, MJ, Meister, S, Duffy, S, Avery, VM, Winzeler, EA, Sinden, RE, Wittlin, S, **Frearson, JA, Gray, DW**, **Fairlamb, AH**, Waterson, D, Campbell, SF, Willis, P, **Read, KD** & **Gilbert, IH** (2016) 'Discovery of a quinoline-4-carboxamide derivative with a novel mechanism of action, multistage antimalarial activity, and potent in vivo efficacy' *Journal of Medicinal Chemistry*, vol. 59, no. 21, pp. 9672-9685. DOI: 10.1021/acs.jmedchem.6b00723

**[R4] Baragaña, B**, **Hallyburton, I**, Lee, MCS, **Norcross, NR, Grimaldi, R**, Otto, TD, Proto, WR, Blagborough, AM, Meister, S, Wirjanata, G, Ruecker, A, Upton, LM, Abraham, TS, Almeida, MJ, Pradhan, A, **Porzelle, A**, Santos Martinez, M, Bolscher, JM, **Woodland, A**, **Luksch, T, Norval, S, Zuccotto, F, Thomas, J, Simeons, F, Stojanovski, L, Osuna-Cabello, M,** Brock, PM,

Churcher, TS, Sala, KA, Zakutansky, SE, Belén Jiménez-Díaz, M, Maria Sanz, L, **Riley, J**, Basak, R, Campbell, M, Avery, VM, Sauerwein, RW, Dechering, KJ, Noviyanti, R, Campo, B, **Frearson, JA**, Angulo-Barturen, I, Ferrer-Bazaga, S, Javier Gamo, F, **Wyatt, PG**, Leroy, D, Siegl, P, Delves, MJ, Kyle, DE, Wittlin, S, Marfurt, J, Price, RN, Sinden, RE, Winzeler, EA, Charman, SA, Bebrevska, L, **Gray, DW**, Campbell, S, **Fairlamb, AH**, Willis, PA, Rayner, JC, Fidock, DA, **Read, KD** & **Gilbert, IH (**2015) 'A novel multiple-stage antimalarial agent that inhibits protein synthesis' *Nature*, vol. 522, no. 7556, pp. 315-320. DOI: 10.1038/nature14451

**[R5]** Patent: **Gilbert, Ian Hugh, Norcross, Neil, Baragaña, Beatriz, Porzelle, Achim** (2013). *Anti-malarial agents* World Intellectual Property Organization. Patent No. PCT/GB2013/050633 (WO2013153357). Available at: https://bit.ly/2ONlQdm (Accessed:27 Nov 2020)

**Key research grants relevant to this case study:**

1. **Frearson, J.A.** Hit discovery in Plasmodium falciparum. Medicines for Malaria Venture (2008-2009). Value GBP40,112
2. **Gilbert, I.H.** Discovery and Optimization of Phenotypic Hits. Medicines for Malaria Venture (2010-2013). Value GBP1,192,000
3. **Gilbert, I.H.** Development of a Screen for the Identification of Plasmodium Falciparum eEF2 Inhibitors. Medicines for Malaria Venture (2016-2017). GBP99,820

## 4. Details of the impact

**Single dose cure molecule targeting multiple lifecycle stages adopted by MMV**
DDU research led to invention of DDD107498 that can treat malaria with a single dose. Crucially, it is effective against parasites resistant to current drugs at a dose within MMV's goal of ~1USD per treatment, affordable in lower-income countries. In 2014, MMV formally declared DDD107498 as a candidate for preclinical development **[E1]**. The discovery won MMV's Project of the Year 2014 **[E2]**. At the time MMV said:

> *"This molecule has caused a stir…. DDD498 has potent activity against multiple stages of the malaria parasite's lifecycle, giving it the potential to cure and stop the spread of the disease as well as protect people, all in a single-exposure"* **[E2]**.

**Incentivising Pharma by de-risking drug discovery**
Developing a new drug costs over GBP1billion. For diseases like malaria, with high prevalence in developing countries, this investment is too high for Pharma, since it cannot be recouped from low-income patients or aid budgets. The DDU's research to invent and characterize DDD107498 incentivized MMV to take it forward through a formal licensing partnership [E4]. In 2015 MMV explained the impact on them:

> "*Thanks to these attractive properties, MMV was able to successfully partner this compound with Merck KGaA…it was licensed their flagship anti-malarial for pre-clinical and clinical development and renamed M5717*" **[E3]**.

Similarly, the Head of Merck Global Health Institute explains the impact on the company:

> "*The DDU's work to identify DDD107498 and characterise it and its safety profile meant that Merck were provided with a highly effective drug candidate ready for clinical trial…The DDU de-risked the process and provided the incentive for us to proceed to clinical development in 2017 with a new drug for malaria that we would have been very unlikely to develop independently. This also allowed Merck to develop our malaria portfolio*" **[E5]**.

Both MMV and Merck benefited by progressing their objective of defeating malaria, thereby encouraging sustained investment. People in malaria-endemic countries benefit from survival of such R&D partnerships working toward malaria treatments and eradication.

**Malaria complete cure in clinical trial with first ever Phase 1 Volunteer Infection Study**
Merck wished to fully understand M5717 (formerly called DDD107498) efficacy earlier than previously possible, due to its promise, and to minimise costs. In 2017, they began novel first-in-human Phase I trials that included volunteer infection studies (VIS) where healthy volunteers received a small inoculum of malaria to investigate M5717 as a clinical cure **[E6].** This was the first time VIS were conducted by a pharmaceutical company as part of Phase I trials. The Head of Merck Global Health Institute confirmed the benefits of this unique study design, prompted by M5717's promise/properties, saying that it *"allowed us to reduce timelines, manage resources and minimize the number of patients needed in Phase II*" **[E5]**.

Merck reported M5717 as **a single dose cure** for malaria at the ASTMH Annual Meeting in 2019, following completion of the Phase I VIS trial. Their abstract confirms that *"Administration of 800 mg M5717 resulted in complete clearance of parasitemia"* **[E7, abstract 1]**. In a recent testimonial **[E5]** Merck confirm the trial demonstrated that M5717:

> *"…could cure subjects with a single dose, which marks a key milestone in its development…The phase I study demonstrated that M5717 has a positive benefit/risk profile and supports its further clinical development as a single dose for the treatment of malaria. M5717 is also active against the liver-stage of the parasite, making it a unique candidate for the prophylaxis and prevention of malaria."*

To this end, a second human challenge Phase 1b trial, initially delayed by COVID-19, has begun to assess the potential not just for cure but for prevention of malaria **[E8]**. The first subject was dosed in September 2020 **[E9]** (trial completes May 2021).

**Unblocking the pipeline of new malaria combination treatments**
WHO recommends combination antimalarial therapy, where each drug has a different mode of action to mitigate against the emergence of resistance. M5717's completely novel mode of action opens up a pipeline towards new malaria combination treatments that partner it with existing or new drugs, and also identifies protein translation/eEF2 as targets for new drug development. Consequent impacts are the sale of DDD107498 to global customers by several international companies to facilitate drug discovery research **[E10]**, and pursuit of combination clinical trials as confirmed by the Head of Merck Global Health Institute:

> "*M5717 is identified as a key asset of the global malaria portfolio and is a central element of the next generation of malaria combinations that are managed by MMV. We are now in the process of identifying a potential partner drug to take M5717 further into Phase IIa.*" **[E5]**.

The Chief Scientific Officer of MMV also explains:

> "*The fact that no-one had previously proposed EF2 as a target for malaria underlines the ground-breaking nature of this discovery…The compounds inhibiting EF2…are the only series we have seen so far…to hit all three* [parasite] *stages equally. This means that any drug will have potential not only for treating malaria, but for protecting against infection, and also to impact transmission…MMV are pleased to acknowledge the significant contribution and impact of the University of Dundee's Drug Discovery Unit in delivering next-generation anti-malarial therapies. The combination of scientific rigour, the entrepreneurial spirit and the deep expertise… has made DDU a triumph of UK science over the last decade…"* **[E3]**.

## 5. Sources to corroborate the impact (indicative maximum of 10 references)

**[E1]** Press release: Medicines for Malaria Venture 2014, 'Potential new antimalarial drug identified at the University of Dundee' *MMV.org.* 6th February 2014.

**[E2]** Press release: Medicines for Malaria Venture 2015, 'MMV Project of the Year award 2014 - DDD498' *MMV.org.* 30th June 2015.

**[E3]** Corroboratory testimonial from the Chief Scientific Officer, Medicines for Malaria Venture.

**[E4]** Press release: Medicines for Malaria Venture 2015, 'Merck Serono and MMV sign agreement to develop potential antimalarial therapy' *MMV.org.* 1st April 2015.

**[E5]** Corroboratory testimonial from the Head of Merck Global Health Institute, Merck KGaA and similar interview from 2018. Medicines for Malaria Venture 2018 'M5717 (formerly DDD498)' *MMV.org.*

**[E6]** Clinical Trial of M5717: Sponsor Merck KGaA 2017, 'First-in-Human Trial of Single Ascending Dose, Multiple Ascending Dose and Malaria Challenge Model in Healthy Subjects' 25th *Clinical Trials.gov* (NCT03261401) 25th August 2017.

**[E7]** Corroboration of Phase 1b VIS clinical trial result: McCarthy J, Bagchus, W, Odedra, A, Webster, R, Oeuvray, C, Tappert, A, Bezuidenhout, D, Yin, X, Khandelwal, A & Yalkinoglu, O. 2019 'A Phase 1b study to investigate the antimalarial activity of m5717, a first-in-class inhibitor of plasmodium elongation factor 2, using the induced blood stage plasmodium falciparum malaria model' *ASTMH* 68th Annual Meeting Abstract 1 p 1.

**[E8]** Clinical Trial: Sponsor Merck KGaA 2020, 'Chemoprophylactic Activity of M5717 in Plasmodium Falciparum Sporozoite (PfSPZ) Challenge Model' *ClinicalTrials.gov* (NCT04250363) 31st January 2020.

**[E9]** News Item: Merck Global Health Institute 2020 'Path to Zero Malaria: M5717 for prevention and cure of this deadly disease' *MerckGlobalHealthInstitute.com* 8th September 2020.

**[E10]** Global Life sciences companies offering DDD107498 for commercial sale and citing **[R4]**: TargetMol Corp. DDD107498, Cat No T5419; ApexBio Technology LLC. DDD107498 Cat No A8711; MedChemExpress. DDD107498, Cat No. HY-117684A*;* MedKoo Bioscience Inc. DDD107498, Cat No. 526858. *Medkoo.com.*