Raising the bar for all future preclinical candidates

MMV’s Project of the Year 2021 is awarded to a discovery team led by Dr Laura Sanz at GSK and Dr Stephen Brand at MMV, for the discovery of GSK4024484 (GSK484), a compound with potential for treatment of patients with uncomplicated malaria. MMV’s independent Expert Scientific Advisory Committee (ESAC) recommended GSK484 for this award owing to its high quality, including its fast and potent antimalarial activity against drug sensitive and resistant strains and ‘irresistibility’ i.e., no detectable resistance selection in vitro, which makes it a potentially important public health tool as part of a future combination to drive the treatment, control and eradication of malaria.

New antimalarial therapeutics are needed to ensure that malaria cases can continue to be treated effectively, as emerging parasite resistance to frontline chemotherapies threatens control programmes in Africa. GSK484, is a novel chemotype which exhibits rapid parasite clearance in vitro and in vivo, and is predicted to have a low dose, when used clinically. This exciting molecule represents a novel structural series, with a mechanism of resistance different to current antimalarials in clinical use and no cross resistance with any compound in the MMV portfolio.

1 A laboratory process that is not conducted in a living organism.
3 Studies in which the effects of various biological entities are tested on whole, living organisms or cells, usually animals, including humans, and plants, as opposed to a tissue extract or dead organism.
Interview with Dr. Laura Maria Sanz-Alonso, Malaria Portfolio Leader, GSK fellow, GSK Global Health Medicines R&D Tres Cantos, Spain and Dr. Stephen Brand, Associate Director, Drug Discovery, MMV; discuss the antimalarial preclinical candidate project.

What are the attributes of GSK484 that make it a promising antimalarial candidate?

Laura Maria Sanz-Alonso – Given the compound’s non-clinical safety profile – demonstrated by a toxicology programme, including selectivity profiles and evaluation of safety pharmacology, genetic toxicology, general toxicology and even developmental toxicity – it has the potential to be considered as a treatment for pregnant women.

Stephen Brand – Because the compound is fast acting, it has the potential to rapidly alleviate malaria symptoms. It is also potent, has a long-predicted half-life in humans and good drug-like properties – these factors combined suggest a very low dose will be required without an expensive complex formulation. The low risk of generating antimalarial resistance and potential for low cost of manufacture further make GSK484 an attractive partner for combination.

Could you briefly describe the project: How did it begin and evolve?

LS – GSK484 belongs to a chemical series, called the pyrazines, which were originally identified by GSK from a P. falciparum intraerythrocytic whole cell phenotypic screening4 conducted in 2010. The many hits5 from that screen were published as a Tres Cantos Antimalarial Set (TCAMS)6 and were the origin of numerous antimalarial programmes both at GSK and externally, particularly in a collaboration between MMV, GSK and Ferrer. Among the different chemical series identified, the promising early properties of the pyrazine hits and their structural novelty led us to prioritize them for a lead optimization programme that ultimately led to the identification of GSK484.

SB – GSK Tres Cantos in Madrid performed a screening of a large collection of GSK compounds against the parasite and identified thousands of hit compounds with good potency against the parasite. From that point, GSK worked on multiple chemical series aiming to improve the many characteristics required to turn them into effective treatments. One of these series, the pyrazines, was particularly interesting because of its irresistibility. After several years of work to improve the key properties, we were able to identify GSK484. The compound was approved in 2021 as a candidate by MMV and our ESAC and is now undergoing preclinical testing before human clinical studies can start.

What key challenges did you face during this project?

LS – The pyrazine series delivered a previous candidate molecule. However, despite its excellent parasitological profile, the previous compound was stopped because of concerns about potential risk of a human anaphylactoid reaction.7

SB – Given the termination of the previous pyrazine candidate, the most significant challenge was to understand the biological mechanism of the safety finding and to apply that knowledge to identify improved compounds without the risk; the team did an outstanding job in solving this, which gives us confidence in progressing GSK484 into pre-clinical and clinical development.

How did collaboration with MMV contribute to the success of the project?

LS – The collaboration between GSK and MMV has been key in identifying this new antimalarial opportunity. The work conducted by both parties as a team, along with MMV’s confidence in the potential of the series and our ability to address the safety risk, enabled us to initiate the back-up project that fortunately led to the identification of GSK484.

How has team collaboration with GSK contributed to the success of the project?

SB – If it weren’t for GSK’s commitment to global health and Laura and her team’s capability in malaria research, we wouldn’t have this candidate. They selected the starting points from their collection, performed the lead optimization and demonstrated tremendous leadership with their early safety studies which allowed them to successfully navigate the real challenges and deliver GSK484.

What has been the impact of this project on MMV’s portfolio and drug discovery process?

SB – This project adds another treatment option to our ever-strengthening portfolio, further increasing the probability of delivering single dose treatments which could ultimately replace artemisinin and other fast-acting drugs. I also believe that this compound is raising the bar for all future preclinical candidates because it has such a strong profile. Ideally, any compound that comes through in the future as a potential candidate effectively needs to be as good as GSK484, if not better.

How does the project fit into MMV’s overarching strategy on resistance risk and improving malaria treatment during pregnancy?

SB – In terms of pregnancy, GSK has already done some preclinical profiling on the compound which suggests that it could be a medicine which is safe during human pregnancies. The compound is also active against parasite strains that are resistant to current antimalarials, and it also appears to be very challenging for the parasite to develop resistance to this compound. It is important to say that these are still early days, and a lot more testing needs to be done, both in preclinical and in clinical development to prove that, but the first signs are promising.

4 Global Phenotypic Screening for Antimalarials. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3269778/
5 A compound which has the desired activity in a compound screen
7 Anaphylactoid reactions are life-threatening events that result from an overactive and misguided immune response to a substance that is viewed by the body as foreign.