7 Enriching the drug discovery pipeline with an 'irresistible' compound

MMV Project of the Year 2019: discovery of novel compound, INE963

MMV's Project of the Year 2019 is awarded to a discovery team led by Dr Thierry Diagana at the Novartis Institute for Tropical Diseases (NITD) and Dr Brice Campo, Senior Director, Drug Discovery at MMV, for delivering a promising new and 'irresistible' preclinical candidate, INE963. The compound is 'irresistible' in the sense that it has not been possible to generate resistance to it in the laboratory.

Decreased activity of artesunate and new resistance to partner drugs in artemisinin-based combination therapies (ACTs), such as piperaquine, has led to treatment failures with some ACTs in South East Asia.[1] New medicines with novel mechanisms of action are thus urgently needed. These should have a low propensity to select for resistance, otherwise their lifespan once deployed in the field will be limited. Experience with ACTs shows that the last day of a 3-day course is often not taken, and this brings two risks. First, the obvious risk is to the patient, who does not receive a full course of treatment, but the second hidden risk is to the drug, since this behaviour increases the probability of resistant parasites developing.

MMV has had a collaboration with Novartis over the last 15 years through the NITD, which recently relocated from Singapore to San Francisco. INE963, approved as a preclinical candidate by MMV's ESAC[2] in 2019 is now the third clinical candidate that has come from the NITD group. It is a very exciting molecule with a number of extremely desirable properties that could make it a potent weapon for combatting resistance as part of a next-generation, reduced-dose combination therapy.

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1 World Health Organization, Q&A on artemisinin resistance, May 2019: https://www.who.int/malaria/media/artemisinin_resistance_qa/en/

2 Expert Scientific Advisory Committee: an external body of experts that helps to identify the best projects worthy of inclusion in MMV's portfolio and continues to monitor progress through an annual review of all projects.

Novartis's INE963 discovery team

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INTERVIEW

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Dr Brice Campo
Senior Director, Drug Discovery, MMV

Dr Diagana and Dr Campo from the INE963 discovery collaboration team tell us more.

Can you tell us about the discovery of INE963?

TD INE963 was discovered through phenotypic screening, in which we screened 1.5 million compounds against the parasite within human red blood cells, without making any prior assumptions about the molecular target. We then filtered the compounds that met these criteria, known as 'hits', to select compounds that were not only effective in clearing parasites from the blood, but also had a rapid onset of action. Several new molecular scaffolds[3] emerged from the screening, and after considerable optimization of one of these scaffolds using medicinal chemistry, we ultimately arrived at INE963 as the candidate of choice.

What are the attributes of INE963 that make it a promising antimalarial candidate?

TD INE963 rapidly kills and clears parasites and stays in the blood for a long time – key characteristics necessary for a potential single-dose cure. The compound does not significantly inhibit cytochrome P450s,[4] meaning that the risk of a drug-drug interaction between INE963 and a partner drug in a future combination therapy is currently low. INE963 also has good oral bioavailability[5] and physical and chemical properties, important considerations that minimize dose size, cost and formulation risks associated with developing a new medicine suitable for use in young children.

BC Importantly, when tested against resistant parasites engineered in the laboratory, as well as known resistant parasites isolated from different malaria-endemic regions of the world, the compound maintains its efficacy. In addition, we have not been able to generate *de novo* resistance[6] *in vitro* in the laboratory to date. Although this does not mean that resistance will never be forthcoming, this is very exciting, since a new compound with a novel mechanism of action and a low propensity to select for resistance has great potential. The next steps for INE963 will be to complete manufacturing, toxicology and GLP-compliant safety studies[7] before progressing to Phase I trials in humans.

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

TD The collaboration between Novartis and MMV started back in 2006, with partners,[8] but this project with NITD[9] was initiated in 2017/2018 following a physical move from Singapore to California, USA. Thanks to the commitment of some critical members of the Singapore leadership team, we rebuilt the team and our infrastructure almost from scratch in Emeryville. Under the leadership of Chris Sarko, Director of Medicinal Chemistry, we are proud that focused collaboration and rapid optimization of the compound series delivered such a high-quality candidate in 2019.

For a disease like malaria with a high global burden and the threat of emerging resistance, we need to stay on top of all new innovations and harvest the fruit of new approaches. By connecting collaborators through its extensive network, MMV captures the breadth of innovation happening in the malaria landscape and helps to inform new drug discovery approaches that we can adopt to develop next-generation medicines; for example, we have been fortunate to benefit from the direct input of Sir Simon Campbell as a mentor from ESAC.[2] MMV's knowledge and experience in malaria, combined with our expertise in drug development, has created a strong and productive partnership.

BC MMV has a long history of collaboration with Novartis and the relationship is extremely strong. Previous front runner compounds from the same chemical series as INE963 have not progressed because of *in vitro* and preclinical toxicity findings. However, the team applied what we have learnt from these experiences to identify a new and better-tolerated compound to move forward to preclinical testing. As Thierry mentioned above, after the start of this project, NITD moved its operational base from Singapore to California, which could easily have slowed, or even halted, progress. However, the new team was established and worked hard to maintain a high level of collaboration and productivity during this transition period, keeping the project on track. The momentum thus achieved was truly impressive.

How does it feel to receive MMV's Project of the Year award?

TD To be recognized as MMV's Project of the Year gives us a great sense of pride, and reflects the exciting potential of this new molecule. It is particularly satisfying to receive the award on the 10th anniversary of Novartis's collaboration with MMV, which began with the discovery of cipargamin back in 2009, for which we received the 2009 MMV Project of the Year!

BC As the MMV project director, I've been part of this team for the past 8 years now. We are a young and passionate team, and I'm delighted that we have been able to deliver a high-quality compound. Going forward, MMV and Novartis will continue to learn from each other, and we hope that many more molecules will come out of this collaboration in the future.

3 A molecular scaffold is the core structure of a compound or series.
4 Many drug–drug interactions are due to changes in the enzyme cytochrome P450 caused by administration of other drugs.
5 The proportion of a drug that enters the circulation when introduced into the body and is therefore able to have an active pharmacological effect.
6 Parasites are challenged in the laboratory with suboptimal doses of a compound for a long period of time to see if resistance develops.
7 Conducted in line with international good laboratory practice (GLP) and good manufacturing practice (GMP) guidelines.
8 Biomedical Primate Research Centre, Singapore Economic Development Board, Swiss Tropical and Public Health Institute, Genomics Institute of the Novartis Research Foundation and the Wellcome Trust.
9 NITD: Novartis Institute for Tropical Diseases, Emeryville, California, USA.

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