

THE right STUFF

Drug discovery can be enormously expensive when a drug becomes a disaster. Professor Susan Charman's team is working to fix potential problems early in the drug-development process.

By Graeme O'Neill

DRUG-DEVELOPMENT COMPANIES SCREEN

hundreds of thousands of molecules, looking for the rare few that exhibit promising activity. But according to Professor Susan Charman, finding a molecule that fits optimally to a target receptor is just the first challenge in drug-discovery. A molecule's pharmacokinetic properties, which determine how it is absorbed, distributed and broken down in the body, must also be fine-tuned to make it a safe and effective drug.

One of the invited speakers at this year's Molecular Approaches to Malaria Conference in Lorne in February, Charman is Professor of Pharmaceutics and Director of the Centre for Drug Candidate Optimisation (CDCO) at the Monash Institute of Pharmaceutical Sciences in Melbourne.

According to Charman, addressing the pharmacokinetic challenges to ensure a candidate drug molecule has a good "developability" profile can be more difficult than discovering the active molecule in the first place. "Even the most potent compound will never be a drug if it can't be effectively delivered and doesn't reach the site of action," she says.

Over the past two decades, there has been considerable emphasis on identifying potentially limiting properties

early in drug discovery. The pharmaceutical industry recognised that poor pharmacokinetic properties contributed significantly to drug molecules failing in clinical trials, with studies showing that between 20 and 40 per cent of investigational drugs that failed in costly late-stage trials did so because of poor pharmacokinetics and toxicity.

As such, researchers developed a range of predictive *in vitro* and *in vivo* methods that now allow a compound's pharmacokinetic liabilities to be assessed at an early stage of drug discovery, ensuring that drug candidates progressing through preclinical development and into clinical trials have a much better chance of success. This is a part of the 'fail early' notion, which would prefer an unsuitable drug candidate be screened out as early as possible rather than accruing the considerable costs of failing during a late-stage clinical trial.

"We typically get involved with drug discovery programs at a very early stage, because the inability to achieve sufficient drug concentrations at the site of action, either through poor absorption or rapid metabolic breakdown, is a major liability for any lead compound," says Charman.



Professor Susan Charman is director and co-founder of the Centre for Drug Candidate Optimisation at the Monash Institute of Pharmaceutical Sciences in Melbourne. A specialist in pharmacokinetics, she has been involved in the development of some of the world's most promising new antimalarial drugs.

"We feed this information back into the chemistry program to identify suitable structural modifications to resolve such liabilities. It's a multidisciplinary process that requires the expertise of chemists, biologists, pharmaceutical scientists and toxicologists, all working together to optimise the necessary properties of a new drug candidate. Getting the balance right and minimising potential liabilities means the drug candidate has much better prospects of actually making it to the market."

While Charman will focus on antimalarial drugs in her Lorne presentation, her team is involved in evaluating a broad range of drug candidates, including anticancer molecules, compounds for CNS disorders and compounds to treat infectious diseases.

SAFETY, EFFICACY

The CDCO team has expertise in drug metabolism and pharmacokinetics, investigating the chemical and structural properties of promising compounds to gain insights into how they the body is likely to tolerate them, whether or not they will be absorbed, how they are distributed, and how long they take to eliminate – all matters central to the safety and efficacy of drugs.

"We work with a number of different groups, including university-based research groups, not-for-profit organisations, and smaller biotech companies that may not have in-house expertise or the necessary infrastructure to assess the metabolic and pharmacokinetic properties of their candidate molecules."

Charman has a particular interest in the discovery of new drugs for neglected diseases, and has had long-standing collaborations with not-for-profit organisations in this area, including the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi), both based in Geneva.

Founded in 1999 with seed funding from the Government of Switzerland, UK Department for International Development, the Government of the Netherlands, The World Bank and Rockefeller Foundation, MMV was one of the first public-private partnerships established to tackle a major world disease. "One of the MMV projects we have been involved with for several years is the development of a synthetic peroxide antimalarial," Charman says.

One of the world's oldest antimalarial drugs, artemisinin, is derived from the Chinese traditional herbal remedy *qinghaosu*, or wormwood (*Artemisia annua*). The active compound contains a unique peroxide bridge that makes the compound, and its derivatives, a potent killer of the deadliest of the five *Plasmodium* species that infect humans, *P. falciparum*.

The collaborative MMV project, involving Professor Jonathan Vennerstrom's team at the University of Nebraska, Dr Sergio Wittlin and his group at the Swiss Tropical and Public Health Institute, Dr Hugues Matile at Roche (Basel), and Charman's group at Monash University, set out to design synthetic drugs around the peroxide bridge motif. Called ozonides, the compounds are cheaper to manufacture than today's artemisinin derivatives, which still rely on extracting artemisinin from the plant as a starting material.

The best compound from the initial discovery program, OZ277, or Arterolane, was the first synthetic peroxide drug tested in humans. India's Ranbaxy Laboratories developed Arterolane further, and recently announced it has secured permission to market the drug in India.

According to Charman, unfortunately the notoriously adaptable parasite is showing signs of possible resistance to artemisinin-based drugs in some areas of southeast Asia, so new antimalarials are desperately needed.

SINGLE-DOSE CURE?

In 2005, the same project team began working on an improved next-generation ozonide based on the same peroxide pharmacophore, but with the aim of developing a single-dose oral cure for malaria. The project team received MMV's Drug Discovery Project of the Year in 2006, and the new drug candidate, OZ439, is currently in Phase II clinical trials.

"Unlike the artemisinin derivatives and Arterolane, OZ439 has very different pharmacokinetic properties that give it an improved efficacy profile in animal models of malaria," says Charman. "We were able to substantially improve its pharmacokinetics by modifying its structure, which changed the way the compound is eliminated from the body."

While the mechanism of action of OZ439 against the parasite is not known, evidence suggests the peroxide bond is activated to produce a carbon-centred radical in the presence of high levels of ferrous iron or heme, which are released when the parasite digests the haemoglobin in red blood cells. The radical is likely to alkylate a number of key proteins, triggering the parasite's death.

"A potential liability of all peroxide-based drugs is that ferrous iron is also present in other regions of the body and



can contribute to the drug's elimination, leading to a short half-life. So the iron is a double-edged sword," Charman says. "By modifying the rate of reaction with iron, we were able to maintain activity against the parasite, yet reduce the rate of clearance.

"Phase I studies in normal volunteers indicated that the half life of OZ439 is considerably longer than that of current artemisinin derivatives and artemether. There is still much to be done, but we are hopeful that one day the drug may be used in the fight against malaria."

Charman's team is working with MMV on several other antimalarial projects. One focuses on a series of compounds called triazolopyrimidines, the lead compound was identified through a collaboration between Professor Meg Phillips' research team at the University of Texas Southwestern Medical Centre, Professor Pradip Rathod's group at the University of Washington and Charman's group at Monash. The project team was awarded the MMV Project of the Year in 2010.

The triazolopyrimidines inhibit dihydroorotate dehydrogenase (DHODH), an enzyme in the pyrimidine biosynthesis pathway, that is essential for the parasite's survival.

CONSORTIA

DHODH is an exciting and promising new target for antimalarial drugs, says Charman. The parasite's enzyme differs from human DHODH in its amino acid sequence, and chemists can exploit these differences to design compounds that will be harmless to humans, while strongly inhibiting the parasite's ability to synthesise pyrimidine bases for its DNA and RNA. The lead compound from this series is currently in preclinical development.

In addition to its work on antimalarial drugs, Charman's CDCO team is a key contributor to an Australian drug discovery consortium involving the Drugs for Neglected Diseases initiative (DNDi) in Geneva, Professor Andrew Thompson and his team at Murdoch University, and Drs Wayne Best and Martine Keenan and their group at Epichem. The consortium is working to identify new drug candidates for parasitic disease including Chagas disease, human African trypanosomiasis, and leishmaniasis. Charman says one of the more promising compounds for Chagas disease will soon be tested in preclinical safety studies.

The group also support the Cooperative Research Centre for Cancer Therapeutics (CTx), which involves the Walter and Eliza Hall Medical Research Institute's Biotechnology Centre at Bundoora, the Peter MacCallum Cancer Research Institute, the St Vincents Medical Research Institute, Griffith University in Brisbane and Adelaide medical biotechnology company Bionomics. "The CTx has a number of drug discovery projects looking at different cancer targets. Some of the early-stage molecules are looking very promising," Charman says.

The huge cost of identifying, testing and developing new drugs has driven the pharmaceutical industry to explore new models for drug discovery. In recent years, there has been a shift away from discovery being conducted largely in-house, with an increasing emphasis on in-licensing of novel molecules discovered in private and publicly funded research laboratories. "This model presents many challenges, but it also provides opportunities for capturing the most exciting and promising discoveries coming out of research groups throughout the world," she says. [ALS](http://www.lifescientist.com.au)