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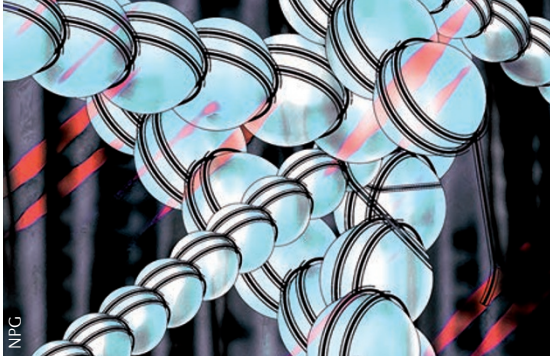

DEAL WATCH

MSD buys in to emerging epigenetic cancer target

Merck Sharp & Dohme (MSD; known as Merck in the United States and Canada) has agreed to acquire and develop a portfolio of inhibitors of protein arginine methyltransferase 5 (PRMT5) from Cancer Research Technology (CRT), in a deal that could be worth up to US$515 million (FIG. 1). These compounds are likely to be investigated primarily for the treatment of blood cancers, but also for haemoglobinopathies.

MSD have a long-standing interest in epigenetics, having brought one of the first epigenetic anticancer drugs, vorinostat — which targets histone deacetylases (HDACs) — to market for cutaneous T cell lymphoma in 2006. Although HDAC inhibitors have struggled to live up to the once-huge expectations of the class (*Nat. Rev. Drug Discov.* **14**, 225–226; 2015), several other families of proteins that mediate epigenetic signalling through acetylation and methylation of DNA have emerged as druggable targets, including protein methyltransferases such as PRMT5.

Stephen Jane's laboratory at Monash University in Melbourne, Australia, identified PRMT5 as an essential repressor of fetal haemoglobin gene expression through research on β-thalassaemia and sickle cell disease. These diseases can be caused by mutations in *HBB*, which encodes the β-chain of haemoglobin. Interestingly, the hereditary persistence of the expression of fetal haemoglobin gene after birth seems to be able to prevent the development of β-thalassaemia in individuals with *HBB* mutations. "So nature has basically said here's a way to fix sickle cell disease on a global scale, if you can work out strategies to reactivate the fetal haemoglobin," explains Jane. His group showed that PRMT5 methylates histones at the fetal haemoglobin gene, thus recruiting DNA methyltransferases, which methylate the gene and silence fetal haemoglobin gene expression (*Blood* **116**, 1585–1592; 2010). They therefore set out to identify small-molecule PRMT5 inhibitors through collaboration with the high-throughput screening facility at the Walter and Eliza Hall Institute, also in Melbourne. The primary aim of developing PRMT5 inhibitors was to treat haemoglobinopathies.

While they were screening, work from other groups had highlighted the importance of PRMT5 and other epigenetic mechanisms in the development of cancer, so Jane took his chemical leads to Cancer Therapeutics Cooperative Research Centre (CTx), an Australian partnership that aims to bridge the gap between academic discoveries and cancer therapies. "This gave us two bangs for our buck — if we were successful in developing inhibitors we would have a potential therapeutic not only for cancer, but also for haemoglobinopathies," says Jane. CTx then screened their own libraries and optimized those compounds for binding and bioavailability. "Once they became engaged, they brought incredibly needed resources to the project, including a large amount of medicinal chemistry," Jane says. "We were also able to attract funding from the Wellcome Trust in the form of a Seeding Drug Discovery Award to underpin the lead optimization of our PRMT5 inhibitors," he adds. CRT, the commercialization arm of the charity Cancer Research UK, became involved at this stage to support the project, assuming commercialization responsibilities and ultimately licensing the rights to develop the PRMT5 inhibitors to MSD.

Although the potential therapeutic role of PRMT5 inhibition in β-thalassaemia is probably due to epigenetic mechanisms, "in cancer it looks as though its targets are not specifically histones — there may be other targets like p53, ribosomal complexes and so on," says Jane. Cheryl Arrowsmith, chief scientist of the Structural Genomics Consortium (SGC) in Toronto, Canada, agrees. "Many of the arginine methyltransferases methylate histones as well as non-histone proteins. Therapeutically, either or both could be important," she says. Her team at the SGC has identified 14 inhibitors of protein methyltransferases, including allosteric inhibitors of PRMT3 (*J. Med. Chem.* **56**, 2110–2124; 2013) and peptide competitive inhibitors of PRMT4 and PRMT6 (*ACS Chem. Biol.*, 24 Nov 2015). Arrowsmith says that "the majority of the inhibitors that have been developed so far for methyltransferases tend to compete with a substrate peptide," but some inhibitors interfere with the binding of the co-factor *S*-adenosylmethionine or disrupt protein–protein interactions within multiprotein complexes, indicating a variety of ways to target the enzymes. "I'm very bullish on the druggability of methyltransferases as a target class," says Arrowsmith.

On the PRMT5 front, MSD is not the only company with commercial interests. Epizyme and GlaxoSmithKline are also developing a PRMT5 inhibitor together and have tested it in preclinical models of mantle cell lymphoma (*Nat. Chem. Biol.* **11**, 432–437; 2015). Clinical trials are expected to start soon.

Importantly for Jane, MSD has also agreed to further investigate these compounds for the treatment of β-thalassaemia. He's glad that the fortuitous role of PRMT5 in a well-funded research area like cancer is enabling the development of potential therapeutics for haemoglobinopathies.

Megan Cully

MSD licenses PRMT5 inhibitors from Cancer Research Technology — Date: 27 Jan 2016

Deal type: worldwide licensing deal	**Value: US$515 million**
• Licensee: Merck Sharp & Dohme (MSD) • Licensor: Cancer Research Technology	• US$15 million cash upfront • US$500 million in milestones • Undisclosed royalties

Asset characteristics
- Inhibitors of PRMT5, a protein methyltransferase implicated in blood cancers and other blood disorders
- Developed by Cancer Therapeutics Cooperative Research Centre (CTx; Australia) with support from Cancer Research Technology and the Wellcome Trust

Focus
- MSD will be responsible for the development and commercialization of the PRMT5 inhibitors
- MSD is also funding a research collaboration with CTx, focused on blood disorders

Figure 1 | **Deal snapshot.** PRMT5, protein arginine methyltransferase 5.