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Latter-stage preclinical developmental work on PL69/DM1157

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The drug class we originally termed 'Reversed Chloroquines' has been assessed, via SAR, to select a candidate for preclinical evaluation. Such molecules were originally designed to function like the late-20th century Gold-standard, chloroquine, but with an appendage that intentionally inhibits resistance. Thus, PL69/DM1157 was subjected to screening, beginning with potency against many laboratory-adapted strains of chloroquine-resistant *P. falciparum* and *in vivo* efficacy in mice. PL69/DM1157, having structural features in common with chloroquine, might have cardiac effects, so we evaluated for hERG interaction, but more rigorously in a guinea pig electrocardiogram model. The results indicated the cardiac safety to be similar to chloroquine.

Academic collaborators have subjected PL69/DM1157 to clinical isolates of highly resistant *P. falciparum*, as well as to *P. vivax* strains. A chloroquine-resistant strain of *P. falciparum* was also subjected to PL69/DM1157 pressure for over two years in an unsuccessful attempt to increase IC_{50}.

The project has now progressed through off-target evaluations, *in vitro* toxicity assessments, and rat preclinical toxicity tests. The molecule has been synthesized under GLP certification, without chlorinated solvents or any chromatographic steps to >99% purity, at sufficient scale to permit final toxicity evaluation in a second species, as well as in a Phase-I clinical trial, using the same batch.

This work also demonstrates how collaboration between a university and a start-up company can be an alternative pathway to bring a neglected-disease drug through the necessary drug development steps. The experience gained through this and other malaria work has enabled the company to begin collaborative work on drug-resistant bacterial diseases as well.

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