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Therapeutics to overcome the differentiation roadblock in Myelodysplastic Syndrome (MDS)

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Scientific Abstract:

Here, we have identified a class of relatively safe, anti-infective small molecule drugs, Artemisinins, as a repurposed mechanism for promoting the differentiation of mutant myelodysplastic cells for the treatment of myelodysplastic syndrome (MDS), a significant and growing unmet medical need. In this application, we describe a preclinical development strategy which leverages the known safety and pharmacokinetics of this drug class to identify a safe and efficacious oral therapeutic agent for treating myelodysplastic syndromes, and further explore its mechanism of action. Specifically, we will evaluate Artemisinins for differentiation inducing efficacy in primary patient derived cells to establish the most responsive patient population and to select a key indication within the broader category of MDS. Likewise, we will use an existing Artemisinin to establish a PK/PD relationship in xenograft models, and we will use medicinal chemistry to optimize a preclinical candidate suitable for chronic dosing in MDS (a profile not yet realized with this class). Lastly, we will use cellular biology and genetics to establish the mechanism by which an off-target activity of this anti-infective class displays potent and highly efficacious differentiation inducing activity in MDS patient derived cells. Overcoming the differentiation roadblock in MDS to restore the normal differentiation pathway could alleviate cytopenias and delay or prevent progression to AML, representing a transformative opportunity for MDS patients. If successful, this application will provide a preclinical candidate for the treatment of MDS, ready for IND-enabling studies.

Lay Abstract:

Myelodysplastic syndrome (MDS) is a pre0cancer condition involving mutations in the stem cells which give rise to the many cell types which compose blood. These mutations cause stem cells to produce red blood cells and other cell types less efficiently, conditions called cytopenias- complications to which most MDS patients succumb. Here, we have identified a class of anti-malarial medications, called Artemisinins, which overcome these mutations, making it such that stem cells can efficiently give rise to downstream blood types, thereby overcoming cytopenias. Artemisinins have been used clinically to treat malaria – the discovery of which was awarded the Nobel Prize in 2006 – but no Artemisinin drug is suitable for chronic oral dosing, which is required for treating MDS. With this grant, we will use medicinal chemistry to develop an Artemisinin derivative that can be orally dosed as therapy for this disease. We will also uncover how an off-target activity of this drug class results in this striking effect on mutated cells. Successful completion of this grant will deliver a preclinical candidate for the treatment of MDS, ready for IND-enabling safety studies, the next steps in advancing this candidate as a new drug.