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**“Toward an assessment of Targeted Osmotic Lysis as a potential novel therapy against Leishmaniasis”**

Leishmaniasis is an often-deadly infection caused by the protozoan parasite, *Leishmania*. It is found mainly in tropical and subtropical areas including South America and Africa. Parasite transmission occurs via the bite of a female sandfly, and around 1.2 million people are infected yearly. Different *Leishmania* species exhibit a variety of tissue tropisms, leading to distinct manifestations of the disease. These include cutaneous, mucocutaneous, and visceral leishmaniasis. As eukaryotes, *Leishmania* share many key biological features with human cells. Thus, the development of effective, non-toxic, parasite-selective chemotherapies against *Leishmania* continues to be a critical medical goal, yet to be achieved.

Given the shared eukaryotic nature of parasites and humans, the challenge of developing effective non-toxic anti-parasitic therapies is somewhat analogous to difficulties associated with developing safe, effective anti-cancer treatments. In cancer patients, cancer cells must retain many biological features of normal human cells, typically making it extremely difficult to selectively target them for therapy.

Recently, studies from the Paul and Gould laboratories at LSUHSC, have exploited the finding that many cancer cells overexpress voltage-gated sodium channels (VGSCs) and sodium pumps, compared to normal cells. To exploit these differences therapeutically, these investigators have developed a novel system that electrically activates VGSCs to allow sodium influx, whilst pharmacologically blocking the sodium ATPase pumps that allow sodium efflux. This strategy results in an excessive build-up of intracellular sodium in cancer cells, resulting in elevated osmotic pressure that preferentially lyses them, leaving normal cells intact. This method is termed Targeted Osmotic Lysis (TOL) and has shown strong clinical promise.

*Leishmania*, as a eukaryote, also has sodium transporters. Further, we recently identified LmjF.34.0480 as a candidate VGSC gene in *Leishmania*. We hypothesize that *Leishmania* may possess functional VGSCs and sodium ATPase pumps that are quantitatively and/or qualitatively distinct from human sodium transporters such that we may use TOL therapeutically against leishmaniasis. To begin testing our hypothesis, our preliminary studies will first, examine the biological effect of different doses of electrical pulsed field exposure upon *Leishmania* viability. Second, we will also examine the effect of different concentrations of Cipargamin, an inhibitor of the sodium ATPase pump PfATP4 in the malaria parasite, upon *Leishmania* viability. Since we have identified a *Leishmania* gene (LmxM.04.0010) that encodes a protein with 50% sequence similarity to PfATP4, Cipargamin may also block sodium ATPase pump activity in *Leishmania*. Following these experiments, we will assess the effect of combining these two treatments to examine whether this causes preferential lysis of *Leishmania* relative to human cells.