Tony Taffaro
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LSU Health Sciences Center, New Orleans, LA

Ben L. Kelly
LSUHSC Department of Microbiology, Immunology and Parasitology

"Examining Charge-dependent Targeting Sequences in *Leishmania* Mitochondrial Protein Import"

Leishmaniasis is a parasitic disease caused by more than 20 species of *Leishmania* protozoa. It is transmitted to humans through the bites of infected female phlebotomine sandflies. The disease primarily impacts vulnerable populations and is strongly linked to poverty, malnutrition, and poor housing conditions. Leishmaniasis primarily affects vulnerable populations in tropical and subtropical regions, although it is also now considered endemic in the Southern U.S. The disease impacts an estimated 700,000 to 1 million people annually. There is currently no vaccine available for leishmaniasis. Furthermore, existing drug therapies face significant hurdles, including high toxicity and rising parasitic drug resistance.

Our research, therefore, is focused on gaining a better understanding of *Leishmania* biology to identify aspects of *Leishmania* cell function that differ from their mammalian host. We are studying the import of mitochondria-destined proteins from the *Leishmania* cell cytoplasm into the *Leishmania* mitochondrion. Our previous studies indicate that the *Leishmania* mitochondrial protein, LmCOX4, is important for *Leishmania* mitochondrial ATP production. Typical mitochondrial protein import in mammalian cells requires imported proteins to have a positively-charged presequence. This allows for mitochondrial membrane potential (ΔΨm)-dependent import, driven by the negative charge of the mitochondrion, established by ΔΨm. Interestingly, *Leishmania* mitochondrial potential becomes diminished following exposure to mammalian temperature (~35ºC), suggesting LmCOX4 import must be less reliant on ΔΨm. Indeed, we recently found that the LmCOX4 mitochondrial targeting sequence (MTS) can mediate mitochondrial protein import in the absence of positively charged amino acid residues. However, studies of another *Leishmania* mitochondrial protein, LdSODA indicated that LdSODA MTS-mediated mitochondrial import is positive charge-dependent. These findings suggest that import, mediated by MTS^{SODA}, should also be ΔΨm-dependent. However, if so, this may be problematic for its import into the *Leishmania* mitochondrion at mammalian temperature, where *Leishmania* ΔΨm is lost. To address this anomaly, we will examine MTS^{SODA}-mediated import of the green fluorescent "reporter" protein (GFP) in *Leishmania* at both insect (27ºC) and mammalian temperatures (35ºC). We will do this using PCR and plasmid expression cloning techniques.