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## Novel Antileishmanial Agents from Natural Sources

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***Novel Antileishmanial Agents from Natural Sources***  
**A Proposal for the Research or Creative Experience for Undergraduates (RCEU) Program**  
**Summer 2015**

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**Project Summary:** The overall goal of this research is to find new chemical agents for the treatment of leishmaniasis. Leishmaniasis is a parasitic protozoal infection caused by several species of *Leishmania*, and is one of the seventeen “Neglected Tropical Diseases” (NTDs) defined by the World Health Organization.<sup>1</sup> There are over 350 million people at risk of infection in *Leishmania*-endemic regions, and mortality and morbidity associated with these diseases is largely due to fragile healthcare systems, lack of access to medicines, and resistance by the parasites to the few current chemotherapeutic options.<sup>2</sup> There is an urgent need to develop new chemotherapeutic agents for treatment of parasitic diseases, and nature continues to be a good source of novel bioactive structures. We have preliminary *in-vitro* antileishmanial screening data that have identified nine Costa Rican plant extracts in our collection with remarkable antileishmanial activity with very low toxicity to mammalian cells.<sup>3</sup> The research will involve collection and extraction of tropical rainforest plants from Monteverde, Costa Rica, that have already shown antileishmanial activity; bioactivity-directed separation and isolation of active compounds; and structure elucidation of novel compounds that show activity. ***We are very experienced in natural product isolation, purification, and structure elucidation.***<sup>4</sup>

The student will be supervised by Dr. Setzer every day, from morning until night, in Costa Rica; and will be supervised every day during the laboratory work at UAH. Dr. Setzer’s office (MSB 315) is directly across the hall from the laboratory (MSB 312) and next door to the departmental computer facility (MSB 317), so he will be available at all times during the day and evenings for consultation. The student’s work will fit directly into the project in terms of new plant species collected and tested, new compounds and activities identified, and dissemination of results by publication in peer-reviewed journals. Dr. Setzer has a good track record in working with undergraduate researchers (more than 160 individuals at UAH) and publishing their results (49 peer-reviewed publications based on undergraduate research have appeared since 2010).

**Student Duties:** There are several areas in which undergraduate student research participation is available.

***Collection and extraction of plants.***<sup>5</sup> The student will participate in our annual field collection trip to Monteverde, Costa Rica. The student will be involved in collection of plant materials under the supervision of Dr. Setzer and our collaborating botanist, Dr. Bill Haber (Missouri Botanical Garden). The student will carry out extraction of plant materials (bark, leaves, or roots) using solvent extraction (Soxhlet extraction using chloroform and then methanol) as well as hydrodistillation of plant materials (using a Likens-Nickerson apparatus) to obtain essential oils. The extraction of plant materials will be carried out under the direct supervision of Dr. Setzer. Our field collection trip is over three weeks. Each morning the REU participant, other students, Dr. Setzer and Dr. Haber will go into the rainforest and identify and collect plants. This is an excellent opportunity for the REU participant to work directly with an expert field botanist/ecologist (Dr. Haber). Each afternoon is spent chopping plant materials and carrying out extractions in our laboratory facility at Hotel El Bosque, Monteverde. All laboratory work in Monteverde is carried out under constant supervision of Dr. Setzer. This is an excellent opportunity for the student to utilize laboratory equipment (Soxhlet extractor, Likens-Nickerson apparatus) that he/she would not otherwise encounter. In addition to plant collection and extraction experience, ***this is an excellent opportunity for the student to experience the tropical rainforest ecosystem and Latin American culture.***

***Isolation of bioactive compounds.***<sup>4</sup> The student will carry out chromatographic separation using both flash chromatography as well as high-performance liquid chromatography (HPLC) to separate the components of crude extracts. We anticipate the student will focus on one of the nine antileishmanial plant extracts that we have identified. Essential oils will be analyzed by gas chromatography / mass spectrometry (GC-MS).<sup>6</sup> This phase of the research will provide hands-on opportunities for the REU participant to become familiar with the

use of several analytical instruments, under the direct daily supervision of Dr. Setzer and project collaborator, Dr. Bernhard Vogler.

**Structure elucidation of compounds.** The RCEU participant will collect and be involved in interpretation of spectroscopic data. We will utilize mass spectrometry (MS), infrared spectrophotometry (IR), and nuclear magnetic spectroscopy (NMR).<sup>7</sup> The student will work very closely with Dr. Setzer and Dr. Vogler both collecting spectral data as well as interpretation to determine structures. In addition to hands-on experiences with the spectroscopic instruments (IR, NMR, MS), the student will become familiar with computer modeling of structure and spectra utilizing several software packages that we have available in our department.

**Molecular modeling of phytochemicals.**<sup>8</sup> After identification of antileishmanial phytochemicals, molecular modeling using the SPARTAN molecular modeling software package will be used to determine the lowest-energy conformations for each of the compounds. Molecular docking using MOLDOCK will then be used to assess potential binding to known *Leishmania* protein targets.

**Manuscript preparation.** Dr. Setzer encourages all undergraduate student researchers to write up their results in the form of a manuscript for publication. The RCEU participant, under the supervision of Dr. Setzer, will help prepare the manuscript(s), which may include data from other undergraduate or graduate students.

**Expected results and deliverables.** Crude plant extracts and essential oils will be collected during our field expedition (May 4-22). Initial preparative flash chromatographic separation of the extract will take approximately one week. Additional chromatographic separation of crude fractions is very variable and depends on the number of components in the mixture, the solvents needed for the separation, and whether the components are crystalline or not. Spectroscopic data for purified compounds are collected as the materials are purified.

**Mentor Supervision and Interaction:** Collection of plant materials will be supervised by Dr. Setzer and our collaborating botanist, Dr. Bill Haber (Missouri Botanical Garden). Extraction of plant materials will be supervised by Dr. Setzer. Training and check out on our GC-MS instrument will be carried out by faculty collaborator Dr. Vogler. Spectroscopic measurements and spectral interpretation will be supervised by Dr. Setzer and faculty collaborator Dr. Vogler. Manuscript preparation will be supervised by Dr. Setzer. We will hold regular group meetings each week. Note: Antileishmanial screening will be carried out by our collaborator, Dr. Lianet Monzote (Pedro Kouri Institute of Tropical Medicine); we are not equipped at UAH to handle pathogenic protozoa; the student will not be exposed to any pathogens.

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